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CHEMICAL STUDIES IN MYASTHENIA GRAVIS *

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PREVIOUS metabolic studies of subjects with myasthenia gravis have dealt chiefly with the inorganic metabolism, particularly that of calcium and magnesium, and with the metabolism of nitrogen, creatine, creatinine, and carbohydrate. The results have been more or less contradictory. Marburg [1] reported a high blood magnesium in one case, but Hellich,[2] and Hellich and Tessenow [3] found that the values for the magnesium of the blood were normal (three cases). Bayha [4] reported a low blood calcium in one case, in contrast to normal values found by Hellich, Hellich and Tessenow, Marburg, Berglund, Medes and Lohmann [5] and Reuter.[6] Laurent and Walther [7] have recently determined values for the potassium of the plasma of six patients with myasthenia gravis. The values appeared to be rather low, but for several reasons, particularly the fact that normal subjects exhibited similar low values, these writers were not inclined to attach great importance to their observations. Keschner and Strauss [8] determined the sugar, uric acid, creatinine, urea, nonprotein nitrogen, and cholesterol in the blood of two patients with myasthenia gravis, and the values obtained for all of these constituents were normal. From more detailed studies of the inorganic metabolism, Pemberton,[9] and Diller and Rosenbloom [10] found negative calcium balances in their cases, and noted that improvement occurred as the result of treatment with calcium lactate. Bookman and Epstein,[11] on the other hand, found the calcium balances of their patients to be slightly positive, and that the administration of calcium lactate caused no improvement. In similar studies, Halpern [12] reported a more marked retention of calcium than that observed by Bookman and Epstein. The results of studies of the nitrogen balance in cases of myasthenia gravis have been of a similar nature. Kauffmann [13] observed a positive nitrogen balance in one subject on a high protein diet during rest and a decrease in this balance as the condition became worse as a result of exercise. Pemberton reported a retention of nitrogen, while Diller and Rosenbloom reported a negative

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nitrogen balance. Halpern [12] reported a marked retention of nitrogen and phosphorus, and Bookman and Epstein generally noted a retention of nitrogen, sulphur and phosphorus.

The excretion of creatine and creatinine by patients with myasthenia gravis has received considerable attention. Berglund, Medes and Lohmann, and Remen [14] reported a definite creatinuria in the cases which they had under observation. Williams and Dyke,[15] and Bernhardt and Simpson [16] observed a creatinuria only in cases in which the condition was severe, while in the cases of Hellich and Tessenow, Gibson, Martin and Buell,[17] and McCrudden and Sargent,[18] no creatinuria was present. Diller and Rosenbloom found low values for the excretion in the urine of creatinine, uric acid, and neutral sulphur, and suggested that the disease is accompanied by a low endogenous metabolism. In addition, Spriggs,[19] Pemberton, and also Bookman and Epstein, reported a low excretion of preformed creatinine. On the other hand, the excretion of creatinine by the patients observed by Curschmann,[20] and of those studied by Hellich and Tessenow, was reported to be normal. It is obviously impossible to draw any definite conclusions from the results reported to date, as to abnormalities in the metabolism of patients with myasthenia gravis.

In a series (Boothby's [21]) of 71 cases we have had the opportunity to study carefully the excretion of creatine and creatinine of 35 subjects with myasthenia gravis, both before treatment and after the beginning of treatment with glycine. Some of the results have been briefly referred to elsewhere,[22] but in connection with a general discussion of the effect of the administration of glycine on the excretion of creatine and creatinine and in the papers dealing essentially with the clinical side of the problem. The more comprehensive data concerning the excretion of creatinine and of creatine in myasthenia gravis will be included in this paper, together with several illustrative case histories.

In addition, we have obtained data for the concentrations of several constituents of the blood of 10 patients with myasthenia gravis. These patients, with one exception, had severe myasthenia gravis. The group included four females and six males, and the ages of these patients ranged from 17 to 69 years. The results are shown in table 1. It is apparent from these data that there is nothing abnormal in the composition of the blood of this group of patients. The values obtained for calcium, magnesium, sodium, potassium, inorganic phosphorus, creatinine, uric acid, amino acid, urea, and sugar were found to be well within normal limits.

The results of our studies on the excretion of creatinine and creatine in cases of myasthenia gravis are summarized in table 2. In general, control periods of two to five days, during which glycine was not administered, were obtained, except in a few cases in which the patients were already taking glycine at the time of their admission to the clinic. After beginning treatment with glycine, data on the daily excretion of creatine and creatinine for periods of usually three weeks or longer were obtained. The daily results

TABLE I

Inorganic and Organic Constituents of the Blood of Patients with Myasthenia Gravis *

Case	Mg. per 100 c.c.									
	Calcium**	Phosphorus**	Magnesium**	Sodium**	Potassium**	Urea N†	Uric Acid†	Creatinine†	Amino Acid N†	Sugar‡
1	11.2	4.2	2.5							
2	10.3		2.2	323	18	15	2.2	1.2	3.1	
3	10.0	4.2	2.1	320	19					
4	10.2	3.0	2.3	330	19	16	2.2	1.1	4.3	90
5	10.4	3.9				12	2.8	1.2		95
6	10.2	3.2	2.2	322	20	15		1.1	4.2	82
7						11	2.9	1.0	3.9	
8	10.0	3.5	2.1	342	20					92
9	10.3	3.5	2.9	323	20	14	2.3	1.2	3.2	79
10	10.0	4.4	2.0	325	20					

* Calcium—Clark-Collip modification of Kramer-Tisdall method.
Phosphorus—Fiske and Subbarow method.
Sodium—Barber and Kolthoff method as modified by Butler and Tuthill.
Urea—Van Slyke and Cullen method.
Uric acid, creatinine, amino acid N—methods of Folin.
Sugar—Shaffer and Hartman method modified by Shaffer and Somogyi.
Magnesium—Modification of method of Denis, using Fiske and Subbarow method to determine P in $MgNH_4PO_4$.
Potassium—Kramer-Tisdall method.
** Determinations made with serum.
† Determinations made with Folin's unlaked-blood filtrate.
‡ Folin-Wu filtrate of whole blood.

for periods of, usually, seven days were averaged; the range of these averages for the time during which glycine was administered is recorded in the table. Throughout the observations the subjects were allowed to take their customary mixed diets. The constant average daily excretion of creatinine and creatine observed after equilibrium had been established on any one regimen suggests that the influence of the intake of food was approximately constant. A few of the subjects were taking ephedrine before the administration of glycine was started, but the response to the administration of glycine appeared to be much the same in these cases as it was in the cases in which ephedrine was not administered.

It is evident from table 2 that the excretion of creatinine and creatine in the untreated patient is not usually abnormal. As a means of comparing different individuals Shaffer [23] has suggested the use of the creatinine coefficient, that is, the milligrams of creatinine, or preferably creatinine nitrogen, excreted per kilogram of body weight in 24 hours. Shaffer presented data which indicated that the creatinine nitrogen coefficient for normal individuals ranges from 5.4 to 11.7, but believed that if inactive, elderly, or obese individuals were excluded, the limits for normal individuals would be approximately from 7 to 11. The creatinine nitrogen coefficients of our male patients ranged from 4.5 to 9.8. If the first five patients, who were

TABLE II

Creatinine and Creatine Excretion of Subjects with Myasthenia Gravis, before and after Administration of Glycine *

Case	Age of Patient, Years	Weight of Patient, Kg.	Glycine Administered Daily, Gm.	Average, Gm. of N in 24 Hours				Creatinine Coefficient**
				Preformed Creatinine		Creatine		
				Before	After	Before	After	Mg. Preformed Creatinine N per Kg. of Body Weight, in 24 Hours
Males								
2	56	57	30–40	0.43	0.42–0.44	0.04	0.02–0.05	7.6
3	69	84	40	0.39	0.33–0.46	0.03	0.03–0.08	4.6
4	63	79	30–40	0.62	0.58–0.72	0.02	0.02–0.06	7.8
6	34	59	30	0.50	0.45–0.50	0.10	0.22–0.26	8.4
8	65	73	30–40	0.49	0.53–0.54	0.04	0.03–0.03	6.7
9	37	73	30–40	0.59	0.57–0.66	0.04	0.01–0.08	8.1
10	19	48	30–35	0.47	0.47–0.47	0.02	0.11–0.15	9.7
11	67	112	30		0.50–0.51		0.05–0.06	(4.5)
12	67	114	30		0.53–0.58		0.01–0.07	(4.7)
13	65	130	40	0.72	0.75	0.08	0.14	5.5
14	69†	89	30	0.56	0.56–0.57	0.03	0.03–0.05	6.3
15	30†	84	40		0.51–0.57		0.23–0.33	(6.5)
16	42	74	30	0.49	0.47–0.55	0.02	0.00–0.11	6.6
17	50†	100	30–40	0.66	0.45–0.69	0.03	0.03–0.25	6.6
18	63	69	35		0.49–0.50		0.07–0.14	(7.1)
19	56†	78	30	0.57	0.56–0.59	0.00	0.02–0.03	7.4
20	24†	64–67	30–40	0.53	0.46–0.54	0.04	0.17–0.26	7.9
21	28	66	20–40	0.53	0.56–0.60	0.02	0.02–0.10	8.0
22	33	69	30–40	0.58	0.59–0.72	0.01	0.03–0.11	8.4
23	48	78	30–35	0.67	0.65–0.77	0.02	0.01–0.12	8.6
24	55	68	30	0.59	0.56	0.03	0.09	8.6
25	40	81	20–30	0.73	0.69–0.79	0.02	0.04–0.15	9.0
Females								
1	35	55	10	0.44	0.38–0.44	0.01	0.01–0.05	7.9
5	17	48	10–20	0.33	0.34–0.36	0.00	0.02–0.08	7.0
7	40†	75	20–40	0.43	0.42–0.44	0.17	0.20–0.28	5.7
26	21	51	30	0.26	0.31–0.36	0.04	0.10–0.20	5.1
27	40†	67	20–30	0.36	0.35–0.37	0.02	0.05–0.14	5.4
28	22†	51	30		0.31–0.35		0.08–0.13	(6.1)
29	24	73	30	0.46	0.48	0.03	0.06	6.3
30	24	71	30	0.49	0.42	0.02	0.13	7.0
31	27	59	30	0.42	0.41–0.44	0.11	0.14–0.16	7.0
32	36	54	6	0.39	0.35–0.37	0.04	0.01–0.05	7.3
33	33	51–55	20–30	0.38	0.38–0.41	0.10	0.09–0.16	7.5
34	55	40	27	0.30	0.30–0.32	0.17	0.16–0.22	7.6
35	24	60	30	0.40	0.41–0.41	0.06	0.12–0.15	6.8

* Creatinine was determined by the colorimetric method of Folin. Creatine was converted to creatinine by boiling with picric acid, and determined according to the method of Folin.

** The coefficients for certain subjects who were already receiving glycine, or to whom glycine was administered immediately, appear in parentheses.

† Patients were taking ephedrine before treatment with glycine was started.

all 65 years of age or more, and obese, are excluded from consideration, the coefficients of the remaining patients will be found to vary from 6.6 to 9.7. This range is somewhat lower than that considered normal for active individuals by Shaffer, and would probably have been still lower if the patients had been on a strictly meat-free diet. On the other hand, there was no such striking deviation from the normal, as has been suggested occasionally for this disease, particularly in view of the fact that the patients were forced to be relatively inactive. The creatinine nitrogen coefficients of the female patients varied from 5.1 to 7.9, a range which is somewhat lower than that observed for the male patients. However, the range of the coefficients for normal women has frequently been considered to be lower than that for men, so that our values do not seem to differ strikingly from the normal.

The occurrence of a creatinuria in our patients before treatment with glycine was started was observed less frequently than might be expected from previous reports. In only two of 18 males who were under observation before the administration of glycine was begun was the excretion of creatine nitrogen greater than 0.04 gm. per day, and in the other patients the excretion of creatine was at most a questionable trace. There was a greater tendency toward creatinuria among the females than among males; five of the 12 female patients on whom control periods were obtained excreted more than 0.04 gm. creatine nitrogen per day. This tendency, as is well recognized, has been frequently noted for normal women. The extent of the creatinuria in the group as a whole showed little correlation with the severity of the disease.

The effect of the administration of glycine on the excretion of creatinine and creatine in cases of myasthenia gravis is shown in table 2. So far as creatinine is concerned, little change usually was observed in the excretion after beginning the administration of glycine. In a few cases a slow, gradual increase in excretion of creatinine occurred, which was accompanied by a definite improvement in the condition of the patient. In many other cases improvement occurred without any change in the excretion of creatinine. In four cases the excretion of creatinine gradually decreased during the administration of glycine; in one of these cases, in which the excretion of creatinine was only slightly reduced, the condition was definitely improved; in the other three cases in which the reduction of excretion of creatinine was more marked, the condition became progressively worse in spite of any type of treatment that could be given. There was, therefore, no clear-cut correlation between the condition of the patients and the changes in excretion of creatinine during the periods in which glycine was administered. In no case was there encountered any abrupt, sudden alteration in the excretion of creatinine.

As regards creatine, the excretion of this substance was almost always increased after the administration of glycine, and in several cases it was markedly increased. Harris and Brand,[24] likewise, observed a slight increase in the creatine excretion in a case of myasthenia gravis in which 22

gm. of glycine were administered per day. Milhorat [25] also has observed that the administration of glycine in cases of myasthenia gravis may increase an existing creatinuria, or provoke one where none existed previously. Some other investigators, who studied only a few cases,[3, 14, 26, 27] have failed to note an increase in the excretion of creatine following the administration of glycine. We have found that the type of change in the excretion of creatine incident to the administration of glycine may vary considerably. Some subjects exhibited an immediate and marked increase in the excretion of creatine, others responded more slowly and gradually, while still others exhibited no response. Because of the slow rate of change observed for many of the subjects, it seems likely that the few who were in this last group would have exhibited some change if they had been under observation for a longer period.

The following reports of cases illustrate these points in somewhat greater detail than the data in table 2.

Case Reports

Case 9. A man, aged 37 years, who weighed 73.1 kg., and whose height was 5 feet and 7 inches (170.2 cm.), had had myasthenia gravis for four months before he registered at the clinic. He had not received any treatment during this period. There was marked weakness of the muscles of the arms, legs, neck, and eyelids, and of the muscles of mastication and deglutition. The patient was so weak that he could barely walk one block, even with help. Improvement, which occurred after the administration of glycine, was approximately 25 per cent in the first two weeks, and approximately 50 per cent at the end of six weeks. At the end of three or four months his condition was still further improved. This improvement has been maintained, and during the last year medication has not been required. He now has been employed at full-time work on the railroad for more than a year. This is the only patient in this series of cases who apparently has been able to maintain his strength completely after medication has been discontinued. The effect of the administration of glycine on the excretion of creatinine and creatine by this patient is shown in table 3. It may be noted that a small but definite increase in the excretion of both

Table III

Effect of Administration of Glycine on Daily Excretion of Creatinine and Creatine in Case of Myasthenia Gravis

	Period of Observation*												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Days in period	2	7	7	7	7	7	8	8	8	10	6	13	8
Preformed creatinine nitrogen, gm.	0.59	0.62	0.60	0.59	0.58	0.57	0.57	0.66	0.63	0.62	0.65	0.64	0.67
Creatine nitrogen, gm.	0.04	0.02	0.03	0.01	0.03	0.03	0.04	0.03	0 08	0.07	0.07	0.06	0.03
Glycine, gm. administered per day	0	30	30	30	30	30	30	30	40	40	40	40	40
Ephedrine, mg. administered per day												48	48

* Periods of observation were consecutive.

creatinine and creatine occurred. The decrease in the excretion of creatine in the last period may have been caused by the ephedrine, which was administered during this time.

Case 16. A man, aged 42 years, who weighed 73.9 kg., and whose height was 5 feet and 10½ inches (179 cm.), had had myasthenia gravis for three or four weeks before he came to the clinic. The condition had progressed rapidly. There was moderate weakness of the muscles of the arms and legs, and of the muscles of mastication and deglutition. He was able to walk several blocks and could eat food without great difficulty. He improved slowly but definitely after the administration of glycine was started, during the two months he remained at the clinic. The daily excretion of creatine increased from a trace to 0.26 gm., and there also was a progressive and definite increase in the daily excretion of preformed creatinine (table 4).

TABLE IV

Effect of Administration of Glycine on Daily Excretion of Creatinine and Creatine in Case of Myasthenia Gravis

	Period of Observation*							
	1	2	3	4	5	6	7	8
Days in Period	2	7	7	7	9	7	7	12
Preformed creatinine nitrogen, gm.	0.49	0.47	0.53	0.55	0.55	0.59	0.61	0.63
Creatine nitrogen, gm.	0.02	0.02	0.00	0.05	0.11	0.23	0.26	0.26
Glycine, gm. administered per day	0	30	30	30	30	30	30	30
Ephedrine, mg. administered per day						16	16	16

* Periods of observation were consecutive.

Further improvement occurred for some time after he left our immediate observation. Then, following a slight relapse, he apparently became discouraged and adopted other treatment. He gradually failed and died about 13 months after he first was seen at the clinic.

Case 25. A man, aged 40 years, who weighed 81.1 kg. and whose height was 5 feet and 9¾ inches (177.2 cm.), had had myasthenia gravis for four months before he came to the clinic. He had not received any treatment during this period. There was moderate weakness of the muscles of the arms, legs, neck, and eyelids, and of the muscles of mastication and deglutition. He was able to walk fairly well, and before he came to the clinic he had been able to work part of each day as a contractor. Definite improvement occurred after the administration of glycine. The improvement was accelerated by the additional administration of ephedrine. He is back at full-time work at present, two and a half years after he first came to the clinic. It has been possible to reduce the dosage of the glycine somewhat, but he notices a weakness when the administration of the drug is discontinued. There was an increase in the excretion of creatine and a slight increase in the excretion of preformed creatinine after the administration of glycine (table 5). The slight decrease in the excretion of creatine observed in periods 6 and 7 may be due to the administration of ephedrine.

Case 20. A man, aged 24 years, who weighed 67 kg. and whose height was 5 feet and 8¾ inches (174.6 cm.), had had myasthenia gravis for nine years before he came to the clinic. There had been partial remissions during this period. Ephedrine, 3/8 grain (0.024 gm.), had been administered four times daily for five weeks before he came to the clinic, but had not produced any improvement. At the clinic, the

TABLE V

Effect of Administration of Glycine on Daily Excretion of Creatinine and Creatine in Case of Myasthenia Gravis

	Period of Observation*						
	1	2	3†	4	5	6‡	7§
Days in Period	2	5	8	7	5	1	1
Preformed creatinine nitrogen, gm.	0.73	0.69	0.73	0.73	0.79	0.75	0.82
Creatine nitrogen, gm.	0.02	0.04	0.15	0.13	0.14	0.10	0.10
Glycine, gm. administered per day	0	20	30	30	30	30	40
Ephedrine, mg. administered per day						16	16

* Periods of observation were consecutive unless otherwise stated.
† Two weeks after period 2.
‡ Two months after period 5.
§ Nine months after period 6.

administration of ephedrine was reduced to 3/8 grain (0.024 gm.) twice daily. A constant intake of food was employed, and food, urine, and feces were analyzed. The nitrogen balance was markedly negative. The additional administration of 15 gm. of glycine, twice daily, improved the nitrogen balance only slightly. The excretion of creatine increased rather rapidly after the administration of glycine and maintained a fairly constant level, except in the ten days during which creatine was administered (table 6). The extra creatine given during this time (period 9) was

TABLE VI

Effect of Administration of Glycine on Daily Excretion of Creatinine and Creatine in Case of Myasthenia Gravis

	Period of Observation*																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Days in Period	4	7	7	7	3	11	9	11	10	7	9	6	5	7	7	8	7	11	12
Preformed creatinine nitrogen, gm.	0.53	0.54	0.51	0.52	0.52	0.52	0.49	0.46	0.47	0.46	0.41	0.43	0.42	0.41	0.41	0.40	0.39	0.39	0.39
Creatine nitrogen, gm.	0.04	0.17	0.19	0.19	0.21	0.22	0.23	0.26	0.54	0.27	0.18	0.26	0.30	0.35	0.27	0.24	0.27	0.27	0.25
Glycine, gm. administered per day	0	30	30	30	30	40	40	30	30	30	30	30	30	30	30	30	30	30	30
Ephedrine, mg. administered per day	48	48	48	48	72	72	48	48	50	gradually increased to									70
Creatine, gm. administered per day †									1										
Eschatin, c.c. administered per day										5 to 20	5 to 20								

* Periods of observation were consecutive.
† One gm. of creatine is equivalent to 0.28 gm. of nitrogen. The extra creatine was quantitatively excreted.

quantitatively excreted. There was a progressive and marked decrease in the excretion of preformed creatinine. The administration of glycine never produced any consistent or material clinical improvement. The patient could not walk and was barely able to turn over in bed. All of his muscles were very weak and he could not raise his head. There was marked difficulty in swallowing which made it necessary to abandon the balance studies and resort to nasal feeding. During the following

five months there was only slight fluctuation in the clinical condition. He never was able to walk more than 20 or 30 steps. He was troubled greatly with mucus in the pharynx. The administration of insulin or eschatin for short periods did not produce any change in the clinical condition, although there were periods in which the intensity of the condition varied. In July 1935, approximately five months after he came to the clinic, he was able to be out of doors in a wheel chair, but he never regained the ability to swallow. He returned home the same month, where he continued to follow about the same treatment as was employed at the clinic. He caught cold, probably pneumonia developed, and he died in the latter part of September.

The changes in the excretion of creatine which followed the administration of glycine are not necessarily characteristic of myasthenia gravis, as we have obtained similar results in many other conditions, such as chronic fatigability, various types of muscular disturbances, and arthritic and rheumatic-like conditions.[22]

Complete balance studies have been obtained in two cases of myasthenia gravis. The detailed results will be reported shortly. In general, the results indicated that the type of balance found depended on the condition of the patient at the time of the investigation. The two patients observed both had very severe myasthenia gravis. Both subjects were taking 3/8 grain (0.024 gm.) of ephedrine sulphate, twice daily, when the studies were started and the administration of ephedrine was continued throughout. One subject, although unable to get around to any great extent without the aid of a wheel chair, had been showing a slow, gradual improvement partly as a result of the administration of ephedrine for several years. She was found to be in nitrogen balance before glycine was administered and maintained this balance when 40 gm. of glycine per day were administered. Nothing abnormal was seen in the sodium, potassium, calcium, magnesium, phosphorus, or sulphur balances, either before or after the administration of glycine. The other patient, who was becoming rapidly worse in spite of the administration of ephedrine, showed a negative nitrogen balance which was somewhat less negative after the administration of glycine. The addition of 30 gm. of glycine (5.6 gm. nitrogen) to the diet failed, however, to prevent a steady loss of nitrogen. Slightly negative sulphur, phosphorus, and calcium balances were also observed in this case, both before and after the administration of glycine.

Summary

The results of metabolic investigations on patients with myasthenia gravis show that the blood contains normal amounts of calcium, magnesium, sodium, potassium, phosphorus, sugar, urea, creatinine, amino acids, and uric acid.

Contrary to many previous reports, no striking abnormalities were observed in the excretion of preformed creatinine, or usually in the excretion of creatine. A definite creatinuria, exceeding 0.04 gm. daily, was observed in only seven out of 30 cases, and the greater proportion of the patients who excreted creatine were women.

The administration of glycine was not followed by any definite, constant, type of change in the excretion of creatinine in the majority of cases. If the excretion of creatinine progressively and markedly decreases, the prognosis may be rather unfavorable. The excretion of creatine subsequent to the administration of glycine was in general appreciably increased.

Balance studies which we have carried out, as well as those of previous investigators, indicate that the condition of the patient determines the type of balance obtained, rather than that any particular abnormality in the metabolism is characteristic of myasthenia gravis.

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METABOLISM OF CREATINE AND CREATININE IN MUSCLE DISEASE *

By A. T. Milhorat and H. G. Wolff, F.A.C.P., *New York, N. Y.*

1. Patients with diseases which affect the skeletal muscle commonly have a creatinuria even when they are maintained on a creatine-free diet. Accompanying the creatinuria, there is usually a diminution in the excretion of creatinine and in the ability of the body to retain ingested creatine (a low creatine tolerance).

2. In progressive muscular dystrophy, often large amounts of creatine are excreted. The level of the creatinuria and the impairment of the creatine tolerance are usually related to the amount of muscle disability. In advanced stages of the disease the creatine tolerance may be impaired to the extent that all of an ingested dose of creatine is excreted in the urine as creatine. The amounts of creatinine excreted are diminished and appear to be related to the amount of functioning muscle still remaining.

The ingestion of glycine for short periods is followed by an increase in the creatinuria and a further decrease in the creatine tolerance. In fact, under these circumstances, the glycine appears to act as an amplifier of defects in creatine tolerance. Moreover, it is sometimes of use in demonstrating less obvious disturbances in creatine metabolism. Such effects differ markedly and are not to be confused with the results of prolonged ingestion of glycine.

In keeping with the widespread and serious involvement of muscles in the infantile and juvenile forms of progressive muscular dystrophy is the severe disturbance in creatine and creatinine metabolism. Not only is the muscle involvement extensive and the disturbance in metabolism severe, but the march of the defect in muscle function and metabolism is rapid. In contrast, stand those patients in whom the muscle disease appears later in life. The muscular deficiency in these subjects progresses slowly, and the disturbances in the creatine and creatinine metabolism are less. The parallelism between the severity of muscle disease and rapidity of progression of the disturbance in metabolism is probably not coincidental.

3. In most cases of myasthenia gravis, only moderate amounts of creatine are eliminated and the creatine tolerance is only moderately impaired. However, patients in whom the course of the disease progresses rapidly to a fatal termination excrete large amounts of creatine and show a more serious defect in the ability to retain ingested creatine. The diminution in the creatinine output appears to be proportional to the loss in the functional capacity of the muscles. The defect in the creatine tolerance can be exag-

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gerated by the ingestion of glycine in patients during an exacerbation of symptoms. Glycine usually has no effect on the creatine tolerance during periods of remission.

4. In amyotonia congenita usually considerable amounts of creatine are excreted. Also, the creatine tolerance is low and the creatinine output is much diminished. Glycine increases the creatinuria and further decreases the creatine tolerance.

5. In myotonia congenita no abnormality in the metabolism of creatine or creatinine could be demonstrated by the methods employed. Like normal subjects, patients with this condition eliminate no creatine or only minimal amounts spontaneously, and are able to retain fairly large amounts of ingested creatine. The amounts of creatinine excreted are similar to those observed in normal individuals of the same weight, sex, and muscular development. Glycine, in the amounts used, is without effect on the excretion or the creatine tolerance.

6. In patients with myotonia atrophica, however, the metabolism of creatine and creatinine is abnormal. There is a diminution in the creatinine excretion which appears to be directly proportional to the reduction in muscle mass. There is spontaneous creatinuria, although the amounts of creatine excreted are much lower than in patients with progressive muscular dystrophy showing similar amounts of muscle disability. In fact, extensive wasting of the muscles and considerable disability of important muscle groups can occur with only a slight or moderate creatinuria. The creatine tolerance is only moderately impaired and is unaffected by the ingestion of glycine. Only in patients showing extreme and extensive involvement of the muscles are large amounts of creatine excreted. The creatine tolerance is then seriously impaired, and the ingestion of glycine is followed by an increase in the creatinuria and a further decrease in the ability to retain ingested creatine. In short, in their metabolism of creatine and creatinine, patients with myotonia atrophica resemble only superficially those with progressive muscular dystrophy.

7. In patients with muscle wasting associated with disease of the anterior horn cells or of the peripheral nerves, the diminution in the creatinine output appears to be directly proportional to the reduction in muscle mass. The amounts of creatine eliminated are smaller than are observed in patients with progressive muscular dystrophy with similar amounts of wasting. Furthermore, the impairment in the creatine tolerance is less than in similarly incapacitated patients with progressive muscular dystrophy. Unless the muscle wasting is extensive, glycine is without effect on the creatinuria or the creatine tolerance. However, when the involvement of the muscles is so extensive as to include most of the skeletal muscles, there may occur defects in the metabolism of creatine and creatinine of a magnitude that equals that seen in advanced stages of progressive muscular dystrophy.

8. The effect of glycine on the metabolism of creatine in muscle disease, as shown in the creatinuria and creatine tolerance, is out of all proportion to the effect of comparable amounts of nitrogen from sources other than glycine and creatine. It is postulated that glycine acts as a precursor of creatine.

9. When creatine is ingested, the absolute amount retained is not fixed but is relative and dependent upon the amount, within fairly wide limits, of creatine administered. The percentage retention, however, is constant. Only when very large amounts are ingested is the amount retained no longer proportional to the amount administered. In these instances, the absolute amounts retained are constant and apparently represent the maximum capacity of the body to hold exogenous creatine.

10. In patients with muscle wasting the total creatinine coefficient (milligrams of creatinine plus creatine per kilogram of body weight) is not constant but diminishes as the incapacity of the muscle advances.

Examination of the data makes it seem probable that a defect in the metabolism of creatine and creatinine may be taken as an index of the total amount of improperly functioning muscle rather than of the amount of wasted muscle. In wasting secondary to cord disease, although certain muscle fibers are completely destroyed by disease, others are perfectly adequate and completely functioning. Moreover, in patients severely affected with wasting subsequent to nerve disease there are commonly regions of the body in which muscle structure and function are adequate and even entirely normal. Under such circumstances clearly evident atrophy may be accompanied by only slightly disturbed creatine and creatinine metabolism. In contrast, primary myopathy may be looked upon as the expression of a general disturbance in the muscle metabolism which affects all or most of the muscle tissue of the body. Furthermore, the actual enlargement of the muscles in certain myopathies, notably progressive muscular dystrophy, makes it especially difficult to correlate visible wasting with the known defects in metabolism. Hence, the necessity is apparent of expressing muscle status in terms of functional capacity rather than of size or postulated structural alterations. It is therefore clear why slight or barely visible atrophy may be accompanied by a severe disturbance in the metabolism of creatine and creatinine.

In brief, in patients affected by a generalized defect in the metabolism of muscle, all of the muscle fibers in the body may be affected chemically without striking visible evidence of wasting until the process has persisted for long periods. On the other hand, patients with striking visible evidence of atrophy may have the bulk of the musculature still in a sound state and hence show minimal evidence of disturbance in metabolism.

Thus, disturbance in creatine and creatinine metabolism and muscle defects are related and sometimes parallel each other. The term muscle

defect does not of necessity imply wasting although this may be present. (In fact the muscle may seem enlarged.) Moreover, in those instances where disease is widespread, notably in primary myopathic diseases, the most serious disturbances in metabolism occur, whereas in the myelopathic diseases in which the muscular involvement is commonly more circumscribed, the metabolic disturbances are less. The exceptions to this general correlation are unusual instances of myelopathic diseases which are so widespread as to simulate the myopathic diseases in their effect on the muscles. In brief, there is a parallelism between the metabolic disturbances and the total mass of improperly functioning muscle.

EXPERIMENTAL THROMBOPENIC PURPURA; CYTOLOGICAL AND PHYSICAL CHANGES IN THE BLOOD *

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WHEN a moderate dose of antiplatelet serum is given to a dog, the animal develops an attack of purpura hemorrhagica, identical in most respects with the human type, and recovers spontaneously. The changes that accompany such a disease in the dog have not as yet been systematically investigated. The observations here presented are the result of a study of some of these changes in a group of 63 dogs in each one of which purpura was produced one or more times.

EXPERIMENTAL METHODS

Cytology. Various methods of counting platelets [1, 2, 3] were tried and the direct method was finally selected. With dogs, when blood was obtained from the ear vein, rapidly handled and with the proper precautions, this method proved to be the most satisfactory. After preliminary shaving and cleaning of the area, the vein was cut with a sharp knife, the tip of the pipette placed against the opening in the vein, and from the freely bleeding wound, blood was aspirated into a 1–200 dilution pipette that had been previously filled with the diluting solution to the 0.5 mark. The diluting fluid was made up of brilliant cresyl blue 0.05 gm., sodium citrate 3 gm., formalin (40 per cent) 0.2 c.c., and distilled water 100 c.c., and the platelets were counted with a high power dry objective and 10X ocular (400X) in a Neubauer chamber. The average of two determinations was taken, if no agglutination was present and if the difference between them was not greater than 8 per cent (technical error for the method) of that average; otherwise the count was either repeated or reported as lost. Erythrocytes were counted in the same preparations and with equal precautions (technical error 5 per cent). The relative number of macroplatelets was recorded by designating as such any platelet that exceeded in length the diameter of an erythrocyte. Preliminary filtering and chilling of solutions, the use of chilled, certified pipettes, and automatic shaking were precautions taken with each count; care was taken to keep all glassware and solutions free of dirt, dust and bacterial contamination, blank counts being performed at intervals on the solutions. Observations on the morphology of the platelets, as well as differential erythrocyte and leukocyte counts, were done on blood smears stained with Wright's stain and buffer solution. Platelets were measured

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along their greatest diameter by means of a micrometer eyepiece, and note was taken of the presence or absence of hyalomere, the type of granules, and quality of the staining reaction. The absolute number of nucleated erythrocytes per cu. mm. was calculated from their percentage in the differential white cell count since no difference can be made out between white cells and nucleated red blood cells in a counting chamber. The *bleeding time* was measured in at least three separate locations at each occasion: the ear vein, the skin of the abdomen, and that of the anterior surface of the thigh. The vein was not cut across but simply nicked at one side; the incisions in the abdomen and thigh were approximately 5 mm. long and 2 mm. deep and were performed by the same operator with a sharp knife after pinching the skin up a little. The edge of a piece of absorbent paper was lightly touched to the surface of the wound at intervals of 15 seconds, or at 30 seconds when the blood was flowing at a slower rate. In all but a few instances, the determination was not continued if it exceeded 25 minutes, being recorded as 25′+. The *mean bleeding time* is the average of at least three simultaneous determinations in separate locations on the same animal. Strictly speaking, its technical error cannot be estimated since each determination involves making a cut in a separate part of the skin, and the location and structure of the skin where the cut is made play a part in the duration of the bleeding. Including such differences, the mean per cent variation between simultaneous determinations performed in normal dogs by the same operator was $\pm$ 21.2 per cent, which rendered multiple, simultaneous determinations imperative. The *coagulation time of the blood* was determined by aspirating venous blood into clean, dry, previously boiled syringes and placing 1 c.c. into each of two clean tubes 8 mm. in diameter, paraffin coated. Clean sharp needles of wide bore and short bevels, and only trained animals with large veins were used. The blood was incubated at 37° C. ($\pm$1°) and clotting was considered complete when the tubes could be inverted without the contents falling out. If the difference between the time taken by the blood to clot in the two tubes was not greater than 15 per cent of the average of the two, the longer time was considered the clotting time; otherwise the determination was discarded if it could not be repeated. *Retraction of the clot* is expressed in units and was estimated by methods described elsewhere [4]; the blood was placed in an uncoated glass tube 8 mm. in diameter, a uniform amount always used (1 c.c.) and the clot observed and measured ½, 1, 2, 24, and 48 hours after being formed. For the determination of the *petechiae reaction of the skin* an automatic device was employed that produced a graded amount of trauma to the skin surface over an area of uniform size. Depending on the number of petechiae brought out five minutes after the trauma was applied, the result was reported as 0, 1, 2, 3, etc.

Whenever indicated, the usual statistical methods were employed [5, 6] in the grouping and analysis of the results. Correlation coefficients were calculated by Pearson's method.[7] For any coefficient that appeared significant,

the correlation *ratio* was also calculated. If there was a *significant* difference between them, the correlation was regarded as non-linear and the ratio taken as its truer measure. A difference was considered significant when it was greater than four times its probable error, as calculated by Blakeman's method.[8] Correlation coefficients and ratios were considered significant when they exceeded six times their respective probable errors. It should be kept in mind that any correlations found do not apply to the whole universe of facts concerning each pair of variables but simply in normal dogs under the specified environmental conditions and at various stages of experimental thrombopenic purpura. Correlations involving the

TABLE I

Numerical Values for the Cytological Constituents of the Blood and the Bleeding Time, Venous Clotting Time and Clot Retraction in Normal Dogs

Determinations	Mean ± P. E.	Standard Deviation ± P. E.	Maximum / Minimum	Coefficient of Variation	Number of Animals	Number of Determinations
Platelets	461,500 ±7,277	141,400 ±5,143	960,000 188,000	30.6%	53	173
Erythrocytes	6,130,000 ±46,884	908,500 ±33,104	9,130,000 4,020,000	14.8%	53	172
Leukocytes	12,287 ±283	5,465 ±202	32,300 3,800	44.4%	53	164
Bleeding time: Ear vein (Minutes)	1.54 ±.04	.905 ±.03	6 .5	58.7%	52	147
Abdominal skin (Minutes)	1.59 ±.05	.943 ±.03	5.5 .5	59.3%	52	130
Skin of thigh (Minutes)	1.48 ±.04	.793 ±.03	4.5 .5	53.5%	52	107
Venous clotting time (Minutes)	17.53 ±.364	3.97 ±.25	30 10	22.6%	6	54
Clot retraction (Units)	2.03 ±.02	.29 ±.01	2.5 .9	14.4%	6	64

number of platelets, erythrocytes, leukocytes, the mean bleeding time, and the skin petechiae reaction were calculated from a group of 414 pairs of determinations each; those involving the venous clotting time and clot retraction, from 139 pairs. In table 1 are summarized the values for the various determinations in normal, unanesthetized, fasting dogs. The size, breed, and age of the animals, the diet and living conditions have been previously stated.[9] The figures for the platelets and erythrocytes show close agreement with those found by Aynaud [10] on 25 dogs. Only slight differences were found in the platelet content of blood obtained without stasis from vessels

in the different portions of the body (marginal ear veins, right and left jugular, cubital and right femoral veins, right carotid artery).

Cytological Changes

Platelets. The rapidity of decline in the platelet level after the administration of antiplatelet serum depended on the route employed. Within two to five minutes after an intravenous injection the platelet count was below 50,000 per cu. mm., and large masses of clumped lysed platelets appeared in the peripheral blood. After an intraperitoneal injection it took from three to five hours for the platelets to reach a low level (chart 1); subcutaneously,

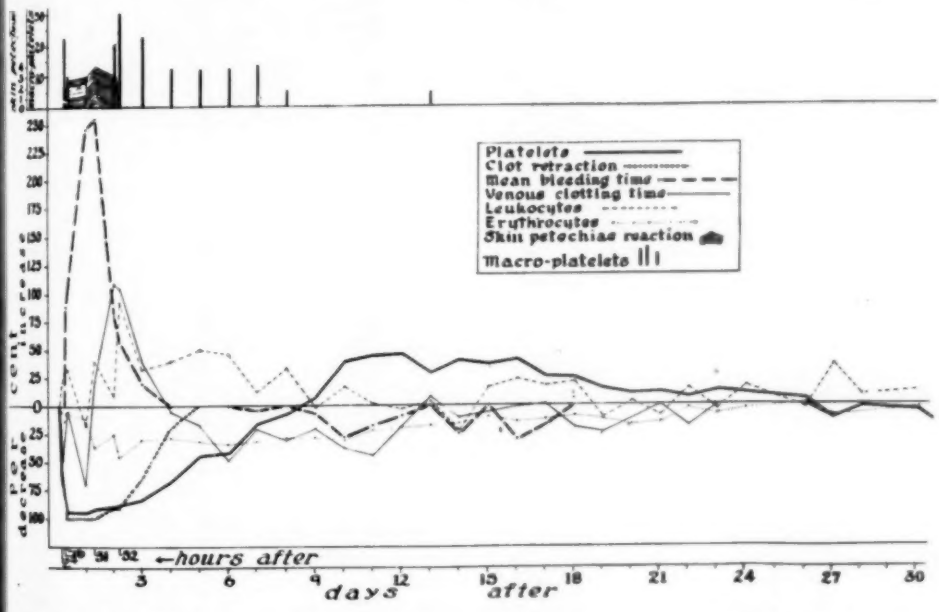

Chart 1. Mean per cent deviations from normal in dogs that received a single intraperitoneal injection of 0.1 c.c. of antiplatelet serum per kg. body weight. (The normal range of values for each animal was ascertained; then the per cent deviation from the upper or the lower limit of this range was calculated for every determination performed at stated intervals after the injection. The curves were constructed from the means of all per cent deviations calculated for each period. Number of animals, seventeen. The curves for the clotting time and clot retraction were derived from seven animals only. Macroplatelets and skin petechiae reaction in absolute thousands and degrees, respectively.)

as long as 12 hours. With a moderate dose the thrombopenia usually lasted 48 to 72 hours, but longer in a few animals. One animal remained thrombopenic for seven days following a moderate dose. The promptness of the recovery was also variable. Most animals regained their previous platelet level three to five days after the last day of thrombopenia and then exceeded it for the next two weeks, the peak being reached from eight to twelve days after the last day of thrombopenia (chart 1). After smaller doses this increase above normal was hardly noticeable. In the few animals

that survived large doses, the thrombopenia lasted many days (18 in one instance). When hemorrhages into the tissues had been numerous and extensive, the platelets reached very high levels. Marked variations in the size and appearance of the platelets were evident both in wet and dry stained specimens. Macroplatelets appeared as early as three to four hours after the administration of the serum intraperitoneally (chart 2), when the num-

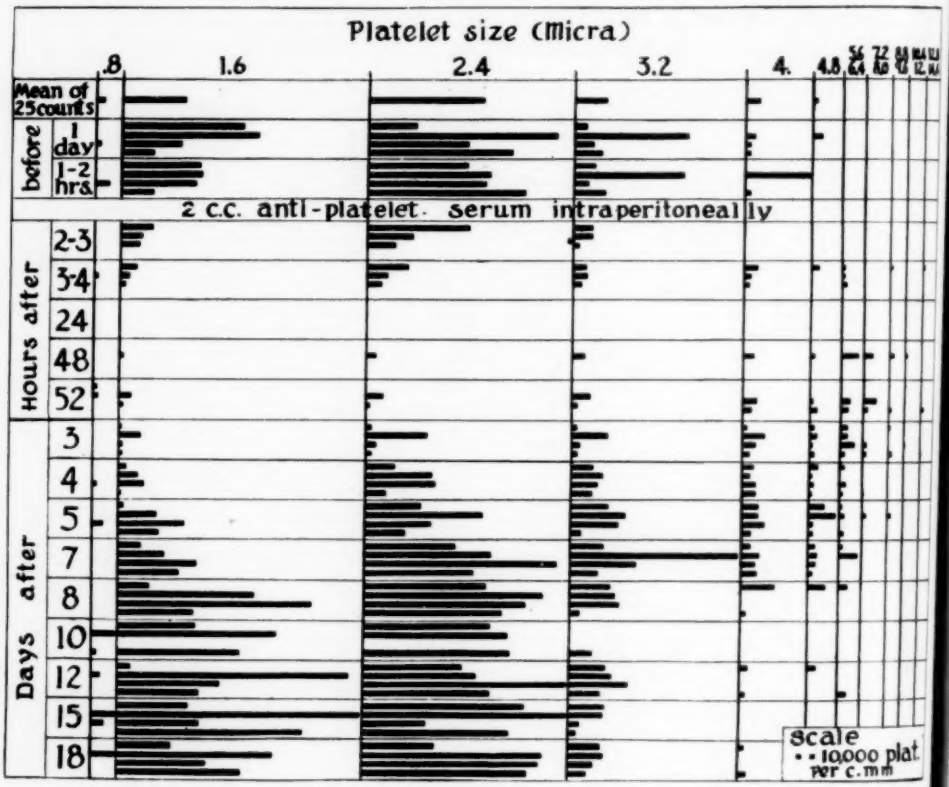

CHART 2. Variations in the size of the platelets of four dogs after the intraperitoneal injection of antiplatelet serum (one count lost on tenth day).

ber of platelets had only been decreased from one-half to two-thirds of their normal level. They were not observed in the next 24 hours but reappeared as the platelet level began rising and were greatest in number from 52 to 72 hours after the injection, when the largest forms were usually seen. For the next four days they decreased steadily in numbers and eventually were replaced by smaller forms. At this stage great irregularity in their size was evident. In contrast to normal platelets, they exhibited no hyalomere, were intensely basophilic and filled with dark, coarse granules; a few had a fimbriated cytoplasm. The appearance of macroplatelets often coincided with the return of the bleeding time to normal and the beginning of the rise in the platelet level (chart 1). Of 17 dogs on which these observations were

made, 10 showed macroplatelets for the first time (during the course of the purpura) simultaneously with the return of the mean bleeding time to normal; 5, with the last long bleeding time determination; and 2, one and two days, respectively, after the bleeding time had returned to normal. Their appearance coincided with the return of retractility to the clot and a diminution in the skin petechiae reaction (chart 1). They were seldom observed in appreciable numbers after the platelets rose to higher levels.

Erythrocytes. After an intraperitoneal injection of a moderate dose, the erythrocytes invariably showed a slight reduction in numbers within 24 hours (chart 1). Decreases were evident during the acute phase of purpura when hemorrhages were prevalent and the bleeding time prolonged. After the hemorrhagic period ceased, they returned slowly to normal. After repeated moderate doses similar observations were made (chart 3). Large

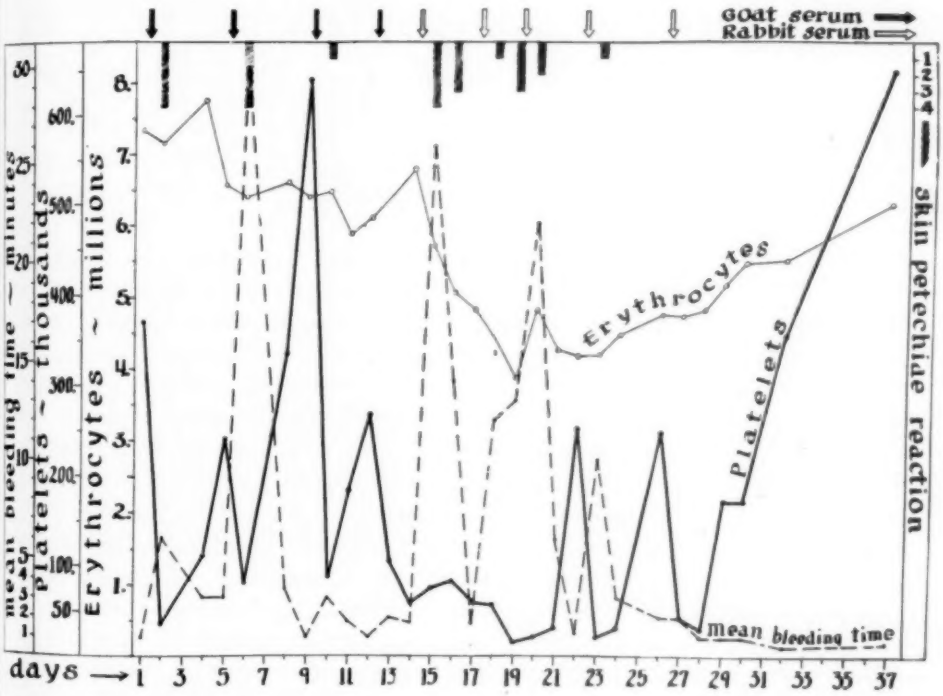

CHART 3. Effect of repeated injections of anti-dog-platelet goat serum followed by repeated injections of anti-dog-platelet rabbit serum in one dog.

doses of the serum and the consequent longer phase of purpura depressed the erythrocytes in four animals to a level below one million per cu. mm. Normoblasts appeared in the peripheral blood following these phases; after a particularly severe hemorrhage in one dog they made up 36 per cent of the total number of red blood cells. Hemolysis in variable degree was always observed in the blood smears during the acute stage of the attack.

Leukocytes. A slight leukopenia often appeared within the first six hours after an intraperitoneal injection. It was generally followed the next day by a leukocytosis which lasted for several days (chart 1). The initial decrease in the leukocyte count took place at the expense of the lymphocytes, monocytes, and eosinophiles, even before the platelets had been reduced to their lowest levels. Twenty-four hours after, those cells began a return to their former level; the monocytes usually went beyond it 52 hours after and the lymphocytes four days afterwards. The eosinophiles did not go beyond the level previous to the injection. The rise in the total leukocyte count resulted chiefly from an increase in the polymorphonuclear neutrophiles. The peak of this rise coincided with the first evidence of an increase in the platelet level of the peripheral blood. As the platelets rose, the polymorphonuclear neutrophiles returned gradually to their previous level, the relative proportions between the other leukocytes not showing any significant changes. An immediate and marked leukopenia, which lasted a few hours, usually followed an intravenous injection of a moderate dose; within the first 5 minutes after such an injection, leukocytes swollen to twice their usual size, enmeshed in clumps of lysed platelets, were often observed in fresh wet preparations of the peripheral blood.

Mean Bleeding Time

With moderate doses intraperitoneally the mean bleeding time first showed a prolongation from three to five hours after the injection (chart 1), sometimes even before the platelets had dropped below 100,000 per cu. mm.; it remained prolonged for 24 to 48 hours, occasionally longer, but rarely more than four days. Cuts made in the oral mucous membrane likewise yielded a prolonged bleeding time during the acute phase. Four minutes after an intravenous injection, a prolongation in the mean bleeding time could be detected. At the height of an acute phase, the ear vein of one of the animals slowly dripped blood continuously for several hours while all about the wound hung thick, stratified blood clots. In animals that survived large doses, a prolongation was maintained for several days, 11 days in two instances. Repeated injections of small or moderate doses at short intervals eventually failed to prolong the bleeding time while still having a destructive effect on the platelets (chart 3). Eventually even the effect on the platelets was lost. Animals differed in the number of doses necessary to bring about this refractoriness. One animal became refractory after one moderate dose; another, after seven such doses.

Normally the bleeding time from the ear vein is greater in volume of output of blood per 15 seconds than that of the skin of the abdomen and thigh. During the acute phase of purpura, the bleeding time of many of the animals exhibited wide variations in the output of blood in a given time interval; a fairly small drop would be followed by one from one-half to five times its size, then large drops appeared in quick succession for the next two

or three minutes with a return to the drops of small size and so on, alternately. The volume output of blood in a given time interval varied remarkably in some instances. A better idea was formed of these variations by collecting the blood issuing from the ear vein at 15 second intervals and measuring it. Various rates of flow were obtained representing normal values (chart 4). During the acute stage the volume output of blood was visibly increased and irregular, whereas after recovery the opposite was observed. Toward the end of the phase of hemorrhages, and one day or more before the platelet count had shown an increase, the bleeding time from the ear vein often showed this peculiarity: after a minute or so of a profuse flow of blood there would be a sudden stop with no subsequent bleeding. When the platelet count was above normal levels the bleeding time became unusually short both in duration (chart 1) and volume of output; often a cut into the skin would yield no blood whatever. It was then that the skin was unusually tense and pale, the fine skin and conjunctival vessels being hardly visible.

Changes in the Coagulation of the Blood. The destruction of platelets by antiplatelet serum injected intraperitoneally produced at first a diminution in the coagulation time of the blood, followed by a period of instability appearing between 28 and 72 hours afterwards and finally by a return to the normal duration (chart 1). After the intravenous administration of the serum the blood also became hypercoagulable during the initial period of platelet destruction (the first few minutes after the injection). That phase was soon replaced by one of prolonged coagulation with a slow return to normal as the platelets reached their former level. A slight prolongation of the clotting time of the blood in rabbits [11] and dogs [12] has been found after intravenous injections of antiplatelet serum, with a slow return to normal accompanying the rise in the platelets. Such was thought to be the usual sequence of events after an injection of that serum. To detect the phase of hypercoagulability, however, it is necessary to collect the blood during the actual period of platelet destruction, or, say, in the first three to four minutes when the serum is given intravenously, and within the first three to five hours when given intraperitoneally. The phase of hypercoagulability is perhaps the result of the great number of destroyed platelets in the circulation; the subsequent period of thrombopenia may partially account for the delayed coagulation.

Clot Retraction. The method of judging this property of the clot depends on the setting of an arbitrary standard for irretractility [4] since platelet-free clots are normally capable of retraction under favorable conditions, as, for example, when forces of adhesion are not dominant. With clots handled under specified conditions, spontaneous syneresis diminished along with the decrease in the number of platelets and was absent when they went below approximately 70,000 (chart 1). It disappeared within the first 10 minutes after an intravenous injection. During the period of purpura, the clots appeared soft, fractured easily, did not hold their shape when removed from

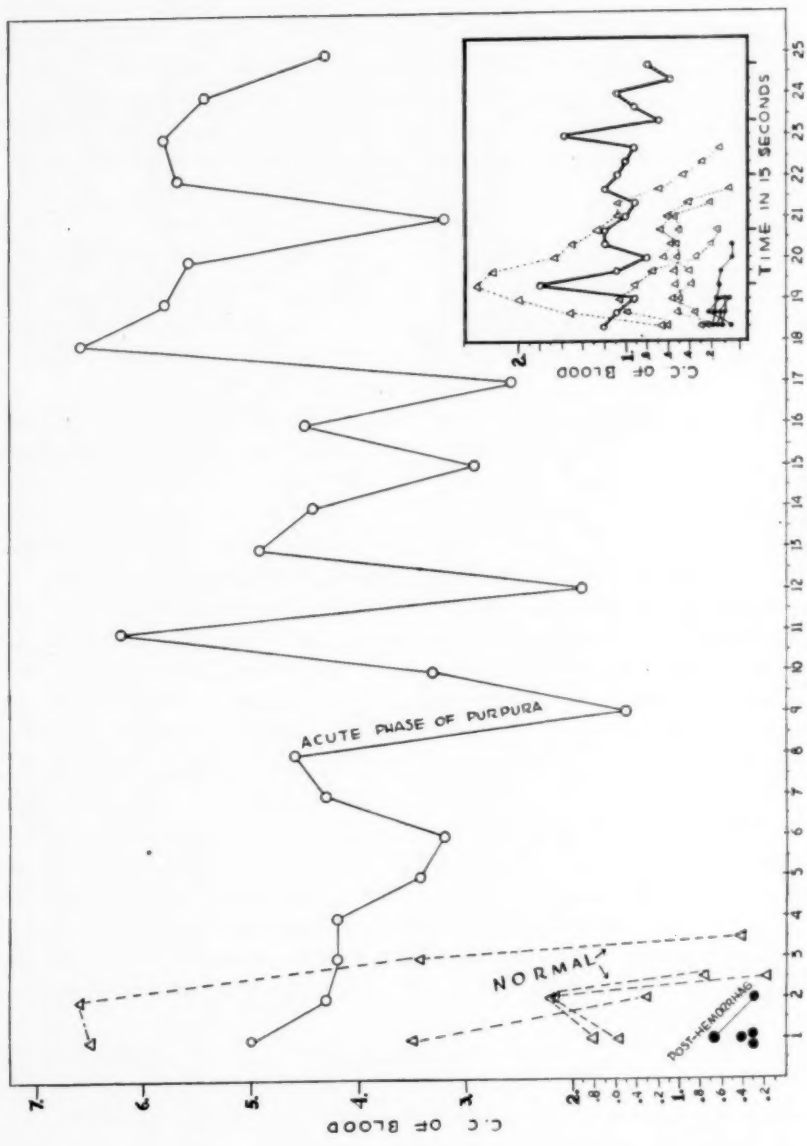

CHART 4. The volume output of blood from the ear vein in a normal dog, and during and after a phase of purpura. Inset: the first five-minute period of the curves in the main graph plotted in terms of the actual amount of blood collected at 15 second intervals.

the vessel, and did not dry for 24 hours and longer. Clots became strongly retractile, however, before the platelets had shown a substantial increase from their low level (chart 1).

Correlations. All correlations were apparently linear since no significant difference could be found between each coefficient and its corresponding ratio, when Blakeman's [8] test was applied. The highest correlation was between the number of platelets and the degree of clot retraction ($+0.759 \pm 0.024$). Second to it was that between the bleeding time and the degree of clot retraction (-0.630 ± 0.04). These two correlations are not higher perhaps because of deficiencies in the method of measuring clot retractility. The moderately high correlation found between the bleeding time and the degree of the skin petechiae reaction ($+0.546 \pm 0.022$) may be traced to the influence of parallel changes in the number of platelets. That the correlation is not higher suggests that these changes alone do not account for the phenomena observed and that other factors must be searched for. The moderate degree of correlation between clot retractility and the skin petechiae reaction (-0.554 ± 0.039) may likewise be traced to changes in a common factor, the platelets, thereby influencing both phenomena simultaneously. There was an inverse correlation, moderately high, between the venous clotting time and the units of clot retraction (-0.462 ± 0.044), which may be explained in a similar manner.

The degree of correlation between the platelets and the bleeding time (-0.424 ± 0.026), and the platelets and petechiae reaction (-0.400 ± 0.027), was lower than anticipated. It was lower than the correlation between the bleeding time and petechiae reaction or between either one of these and clot retraction. This points to a closer relationship of the bleeding time and petechiae reaction with the character of the clot than with the platelet level of the blood. The diminution in the retractile power of thrombopenic clots may be related to the diminution or loss of elasticity of the skin observed during the height of an attack of purpura.

The similarity in degree between the coefficients for the platelets and bleeding time, and the platelets and the petechiae reaction suggests that whatever factors, aside from the platelets, influence the bleeding time, perhaps also play a part in the skin petechiae reaction. The relatively lower degree of these two correlation coefficients is another point favoring the existence of these other factors. There was a low correlation, not significant, between the mean bleeding time and the clotting time ($+0.113 \pm 0.056$); this helps to reinforce the impression obtained clinically that changes in the coagulation time of the blood have very little effect on the bleeding time. There was likewise a useless correlation, of no significance, between the number of platelets and the clotting time of the blood (-0.234 ± 0.069). This indicates that, although the platelet undoubtedly plays a part in the coagulation of the blood, this phenomenon is so complex that the rate of coagulation cannot be predicted from the number of circulating blood platelets alone. It also suggests that whatever disturbances in hemostasis were

of purpura. Inset: the first five-minute period of the curves in the main graph plotted in terms of the amount of blood collected at 15 second intervals.

the result of the destruction of platelets, changes in the coagulation of the blood did not contribute a large share in originating or perpetuating them.

Discussion

If macroplatelets may be considered as evidence of increased or abnormal platelet regeneration, it is clear that this may begin within from three to four hours after the platelets have been moderately reduced in numbers by the antiplatelet serum. Their subsequent disappearance and absence during the next 24 hours may be evidence that the young forms are destroyed by the circulating anti-serum or that no new forms can be regenerated because of a disabling effect of the serum on the thrombopoietic tissues. Perhaps the initial effect of the serum on these tissues is a stimulation to greater activity, followed by a depression during which no giant forms are observed. The uniform rhythm of their appearance also argues strongly against the proposed theory that "in vivo" the platelets are not destroyed by the serum [12] and that their disappearance from the peripheral blood is only temporary. If these forms bear a relationship to the mature platelet similar to that of the reticulocyte to the red blood cell, then the response of the marrow to a sudden decrease in the number of circulating platelets is approximately as rapid as the response of reticulocytes after a hemorrhage. Steele [13] found that the reticulocyte percentage of rabbits bled out of 35 per cent of their blood, increased within a few hours after the bleeding.

The variations in the volume output of the blood from wounds during the various stages of purpura suggest changes in the normal distribution of blood among the vessels or alterations in their caliber, or in the pressure within them. A bleeding time shorter than normal appears to have been previously recorded only by Russell [14] in canaries with chronic malaria.

The correlation between the number of platelets and the bleeding time was not as high as might have been expected. This is perhaps because: (*a*) The number of circulating platelets may not give a true idea of the actual number of available functioning platelets in the blood at a given time. An increased utilization of platelets may take all the platelets being regenerated and leave no balance to swell the numbers in the circulation; this would explain the low platelet count with a normal bleeding time, if the latter were almost exclusively a function of the platelets. (*b*) Collateral forces of hemostasis of a vascular or extra-vascular nature may take a hand in the control of the bleeding during the thrombopenic interval. The demonstration of the presence and nature of such forces is difficult until more extended studies of the vessels are available. The return of the tonicity of the skin to normal before the platelets have reached a high level may partially account for the diminution in the bleeding time. With two exceptions, no really high correlations were found, which emphasizes the complexity of the mechanism of hemostasis and the multiplicity of factors involved in maintaining its integrity. Among these factors should be considered the permeability of the vessels, the capillary and venous pressure, the colloid osmotic pressure

and viscosity of the blood and the tension or elasticity of the tissues adjacent to the vessels. These forces are known to play a part in the movement of fluid to and from the vessels; it is natural to suspect them of influencing the escape of blood.

SUMMARY

Various cytological and physical changes in the blood of dogs with experimental thrombopenic purpura are described and an analysis made of the extent of the correlation between these changes themselves and the external manifestations of the disease.

Morphological variations in the platelets were regularly observed soon after a diminution in their level in the peripheral blood as well as preceding their return to normal after a period of thrombopenia.

The volume and rate of output of blood per unit time from a skin wound were increased and irregular during the acute phase of purpura and became markedly decreased in the first few days following recovery.

The highest correlations found were between the number of platelets and the degree of clot retraction, and between the latter and the mean bleeding time.

The correlations were of such a degree as to indicate that other factors than those under analysis will be found to play important rôles in the mechanism of normal and impaired hemostasis.

I am indebted to Drs. Thomas McCrae and H. W. Jones for their sympathetic support and to Miss Katherine Pierpoint for efficient technical assistance.

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A COMPARISON OF THE RATE OF ABSORPTION FROM NORMAL AND BURNED TISSUES *

By Edward C. Mason, M.D., F.A.C.P., Pearl Paxton, M.S., and H. A. Shoemaker, Ph.D., *Oklahoma City, Oklahoma*

In 1925, Mason, Davidson et al. published a series of papers,[1, 2, 3] recording the observations made on animals which died in 15 to 18 hours as a result of a small piece of liver tissue left free within the abdomen. While doing this work, we conceived the idea that death following burns was probably due to the same factors which caused the death of these animals. Davidson,[4] at the suggestion of Mason, introduced the tannic acid treatment of burns on the assumption that tannic acid would precipitate the dead and dying tissues and thereby prevent the absorption of toxic materials. The splendid results obtained by Davidson, and subsequent workers, apparently justified our theory.

The theory of toxic absorption accompanying burns has been held by numerous authors, and a variety of substances has been claimed responsible for the cause of death following burns. A very comprehensive list of such substances may be found in the paper of Fender,[5] on the subject of "Lymphatic Pathology in Relation to 'Toxins' of Burns." More recently, Underhill [6, 7, 8, 9] expressed the idea that no absorption occurred from burned areas, and in support of this contention he presented data which showed delayed absorption of such substances as strychnine and phenolsulphonephthalein from burned areas. From his observations he concluded that within a period of less than two hours following a burn there is a marked increase in permeability. "The increased permeability of capillaries appears to be in one direction only; namely from the blood to the tissue fluids. From the tissue fluid to the blood there is an apparent decreased permeability." [7] As a result of his studies, Underhill stressed the replacement of body fluids, lost from the burned area, as the principal therapeutic measure. He considered that the local treatment of burns was of secondary importance. We have continued the study in order to determine if substances other than strychnine and phenolsulphonephthalein are absorbed from burned areas. We have selected potassium iodide, a readily diffusible substance of relatively low molecular weight, and have studied the rate of excretion following subcutaneous injections in normal and burned animals.

Experimental

Normal rabbits were used to determine the rate of excretion of potassium iodide injected beneath the skin of the abdomen; the amount of potas-

* Presented before the American Physiological Society, Detroit, Michigan, April 13, 1935.

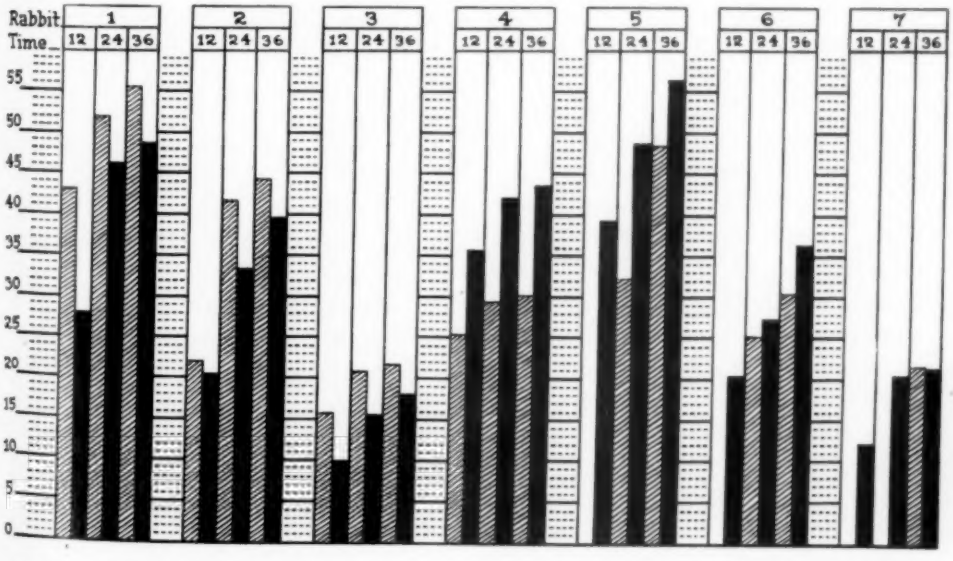
From the School of Medicine, University of Oklahoma.

sium iodide being 5 c.c. of a 2.29 per cent (approximately isotonic) solution per kilogram of body weight. The per cent of potassium iodide excreted by such normal rabbits varied greatly, the greatest total excretion for 36 hours being 55.4 per cent of the total potassium iodide injected, while the lowest was 21.7 per cent. Repeating the determinations, we found that animals which excreted a high percentage on the first test also excreted approximately the same amount on the second test and, likewise, those excreting a low percentage on the first test also excreted a low percentage on the second. The urine was collected by catheterization each 12, 24 and 36 hours following the injection. The amount of potassium iodide excreted was determined by a method developed by one of us (H. A. S.[10]) which is an adaptation from a variety of existing methods. Briefly, the method includes the destruction of the organic material by oxidation and the conversion of the iodide to iodate by bromine water in a slightly acid solution. Potassium iodide is added, and the liberated iodine is titrated, using sodium thiosulphate with starch as the indicator.

While the animals were completely anesthetized, a burned area was produced on the abdominal surface, and six hours following the burn, potassium iodide was injected subcutaneously in the burned area, the amount of potassium iodide used being the same per kilogram of body weight as was injected into the normal rabbits.

The data obtained from the normal and burned rabbits appear in the following table.

THE RATE OF EXCRETION OF IODIDES ABSORBED FROM NORMAL AND BURNED AREAS



The cross-hatched bar represents iodide excretion by the normal animals.
The solid black bar represents iodide excretion by the burned animals.

The values are expressed as the total per cent of potassium iodide recovered at the end of 12, 24 and 36 hours. It will be observed that the excretion is essentially the same in both the normal and burned animals. Three rabbits excreted slightly more in the normal state and three excreted slightly more in the burned state. While one animal's output was practically the same before and following the burn, this rabbit No. 7, developed a respiratory infection during our study and died shortly after the completion of the experiment. No urine was obtained from rabbit No. 6 by catheterization at the end of the first 12 hours, and none was obtained from normal rabbit No. 7 for the 12 and 24 hour periods; however, by washing the cage and collecting the total output, we obtained results quite comparable to the other rabbits.

Discussion

The experience during the late World War demonstrated the fact that the absorption of extracts of freshly crushed tissue and extracts of autolyzed tissue caused toxic symptoms. The generally accepted treatment became that of debridement, and the results verified the contention that a wound freed of dead and dying tissue gave the patient a better chance for recovery. This theory was also strongly supported by the studies of Cannon [11] on wound shock.

More recently this old conception has been attacked,[12, 13] and evidence has been presented to support the theory that with the presence of injured tissue injured either mechanically or by burning, there occurs an outpouring of body fluid into the injured area; and such fluids represent blood serum or blood plasma. It is further claimed that the resulting blood concentration will account for all the symptoms and pathological changes which occur in " secondary shock."

In support of the older idea of " wound shock," Mason and Nau [14] have recently presented evidence that the absorption of products of autolysis of sterile liver does produce definite pathological changes within the host. Also, the marked decrease in mortality,[15] from 28 to 15 per cent, resulting in the use of tannic acid in the treatment of burns suggests that the toxic material is precipitated by the tannic acid and its absorption prevented. Quite recently Blalock has agreed that the absorption of extracts of injured tissue (burned tissue) may be the cause of shock. The following quotation is taken from his discussion.[16] " First, I would like to state that I believe some instances of shock are due to the absorption of toxic products. The action of toxic material is probably the main factor in producing death in the patient who has intestinal obstruction with strangulation of the blood supply. I believe that deaths which occur from three to ten days following severe burns are due in large part to the absorption of protein decomposition products."

Conclusions

1. A readily diffusible substance of low molecular weight, such as potassium iodide, is absorbed from burned areas.

2. Death occurring several days following severe burns is due mainly to the absorption of protein decomposition products.

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STUDIES IN MULTIPLE SCLEROSIS

VIII. ETIOLOGIC FACTORS IN MULTIPLE SCLEROSIS *

By TRACY J. PUTNAM, M.D., *Boston, Massachusetts*

THE EXPERIMENTAL PRODUCTION OF LESIONS SIMULATING MULTIPLE SCLEROSIS

IN previous communications, it has been pointed out that lesions closely resembling typical plaques of multiple sclerosis may be produced in animals in either of two ways: by the subcutaneous injection of minute doses of tetanus toxin [1] and by experimental obstruction of cerebral venules.[2] In each case sclerotic lesions could be demonstrated only after an interval of several months from the original injury. The earlier lesions closely resembled those of "post-infectious encephalomyelitis," a disease occasionally seen following measles [3] and vaccinia [4] and often without obvious antecedent. Areas of demyelination, with relative persistence of axis cylinders, accompanied by infiltration in the early stages and gliosis later, have also been described as a result of carbon monoxide poisoning with venous thrombosis,[5] and chronic cyanide poisoning.[6]

By themselves, these experimental results prove little in regard to the human disease of multiple sclerosis. They do suggest, however, that:

1. "Post-infectious encephalomyelitis" and multiple sclerosis may represent the same pathologic process at different stages with variations in intensity.

2. Local anoxemia, or more specifically local venous obstruction, should receive consideration as the immediate cause of the primary demyelination.

3. The process may be precipitated in some way by an organic toxin, and probably by any one of many.

None of these propositions is entirely new, but apparently no attempt has been made to interrelate them. Indeed, they have been considered almost mutually exclusive. Thus multiple sclerosis has been looked upon as a toxic disease, and therefore not circulatory, or as an infectious disease and therefore not toxic. Before attempting to harmonize these points of view, let us see what may be said for each of them separately.

"ENCEPHALOMYELITIS" AND MULTIPLE SCLEROSIS AS MANIFESTATIONS OF THE SAME PATHOLOGIC PROCESS

The essential similarity between "encephalomyelitis" (especially the post-measles and post-vaccinal forms) and multiple sclerosis has frequently

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been affirmed,[7] and almost as frequently denied.[8] The points of similarity between the two diseases which are usually pointed out are the patchy distribution of the lesions, which surround venules of the white matter, and the predominant involvement of myelin, axis cylinders often remaining relatively intact. On the other side of the question, it has been asserted that the lesions of the acute disease are more diffuse than those of multiple sclerosis, and this is doubtless true in some instances. In these cases the picture as a whole is much more similar to that of diffuse sclerosis or Schilder's disease. This condition, however, is probably to be considered a variant of multiple sclerosis.[9] Further, it has been objected that there is much more extensive loss of axis cylinders in the lesions of " disseminated encephalomyelitis " than in typical sclerotic plaques. This is probably true, but it must be remembered that the patient has died at the height of a severe acute process in most cases of the former disease coming to autopsy, while a milder process, such as multiple sclerosis, might be expected to allow the survival of axis cylinders in greater numbers. Even in multiple sclerosis, extensive loss of axis cylinders is common, as all modern investigators have reported. In a series of 35 separate plaques from 11 cases of multiple sclerosis studied with this question in mind, almost complete destruction of axis cylinders was found in eighteen.[10] A case reported by Walthard [11] is often cited as direct evidence that post-measles " encephalitis " is not the equivalent of multiple sclerosis. The patient died three months after a typical onset, and at autopsy a considerable loss of axis cylinders was found in most of the lesions. Perhaps more relevant, however, may be the cases of Cramer [12] and of Schlesinger,[13] in both of which the patients survived an unmistakable post-infectious " encephalitis " for many months and in both of which typical sclerotic plaques (figure 1) containing relatively intact axones were found post mortem. Walthard's case may then be considered a transitional form of which a number have been reported.[8, 14, 15]

Gliosis, which is a striking feature of multiple sclerosis, would scarcely be expected in an acute process. It is, however, not as specific for multiple sclerosis as has sometimes been supposed. Lesions with loss of myelin but with little or no gliosis occur side by side with typical sclerotic plaques, and on the other hand, areas of secondary degeneration in other pathologic conditions of comparable age and intensity with those of multiple sclerosis develop quite as dense a glial scar. (Figures 2 and 3.) It is probably a general rule that once myelin has been broken down, it cannot regenerate in the adult central nervous system,[16] and that myelin loss is repaired by a glial fibrosis which grows denser and less cellular with the passage of years. An exception to the rule is seen in such conditions as the degeneration accompanying primary anemia, in which gliosis appears to be inhibited by some nutritive lack.

Additional points of similarity between " encephalomyelitis " and multiple sclerosis, which have apparently escaped notice, are the vascular ob-

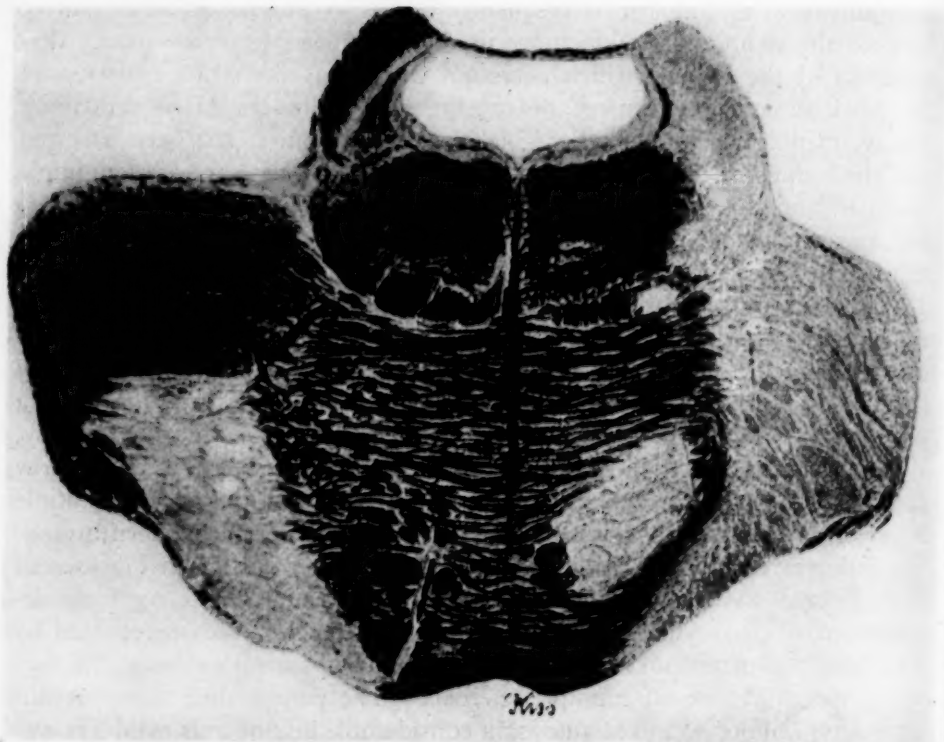


FIG. 1. Typical sclerotic plaques in the pons, from the brain of a boy of 7, who died 22 months from the onset of a clinically typical post-measles "encephalomyelitis," after a course marked by remissions and exacerbations. (After Schlesinger.[13])

structions and engorgement and the perivascular hemorrhages seen in both, as will be described below.

It is assumed by most writers on the subject, often without any display of evidence, that an "encephalomyelitis" in which an infiltration with hematogenous cells occurs must be due to a filterable virus if it occurs in the course of a virus disease. Infiltration with lymphocytes and leukocytes is, however, common in the vicinity of softenings and tumors.[17] Further, Rivers [18] has pointed out that all known virus diseases lead primarily to either a necrosis or a proliferation of parenchymal cells, or both, while in "encephalomyelitis" of the type in question the chief damage is to cell appendages, and in particular to the myelin which is probably to be considered as intercellular substance.[19]

VASCULAR LESIONS AND DEMYELINATION

In addition to the experimental data already presented, there is evidence from the pathology of other diseases that disturbance of circulation may lead to loss of myelin and to gliosis. Thus the ordinary forms of arterio-

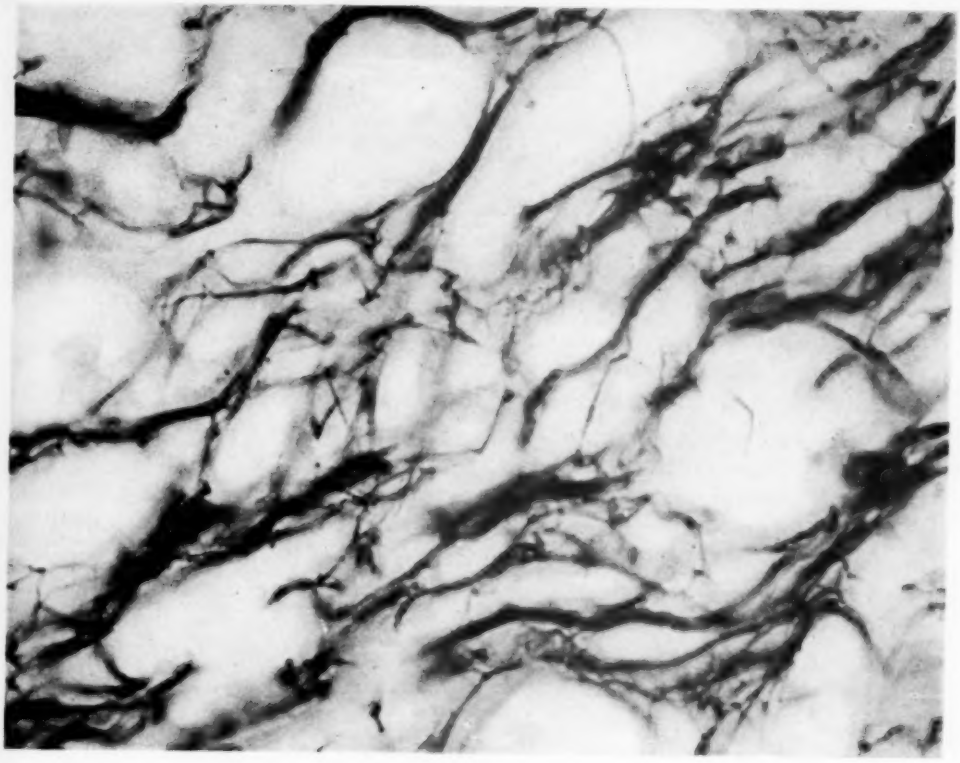
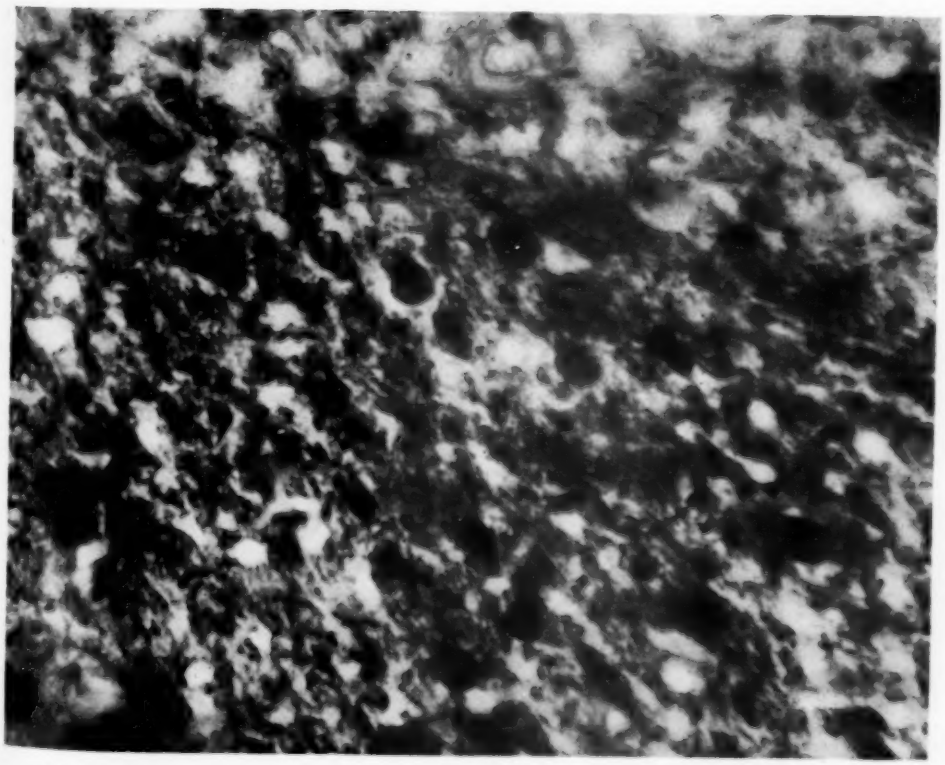


FIG. 2.



FIGS. 2 and 3. Loose, filmy gliosis (figure 2) from a plaque from a long-standing case of multiple sclerosis, for comparison with the dense gliosis in a degenerated pyramid (figure 3) secondary to a capsular apoplexy 10 years previous. Note also the absence of axis cylinders in the sclerotic plaque. Masson stain, oil immersion lens.

sclerosis may produce small lesions in the nervous system in which the myelin suffers far more than the axis cylinders. In human as well as in experimental carbon monoxide poisoning, areas of demyelination may be situated in relation to thrombosed veins,[5] and in one well studied case, exposure to carbon monoxide apparently precipitated a fatal exacerbation of multiple sclerosis.[20] In the condition known as chronic subcortical encephalopathy, plaques closely resembling those of multiple sclerosis occur obviously as a result of vascular obstruction.[21]

Alterations in the blood vessels have long been recognized in multiple sclerosis, and formerly a good deal of emphasis was laid upon them as possibly of importance in the etiology of the disease; for example, by Williamson,[22] Ribbert,[23] and Borst.[24] It was usually assumed that the vascular abnormality permitted the escape of a toxin or " toxic lymph " into the substance of the brain. More recent writers, such as Hassin,[25] have dismissed the vascular changes as secondary to the parenchymal degeneration. The perivascular infiltration may well be accepted as the cause of adventitial proliferation, but it seems open to question whether the obstructions, dilatations, and perivascular hemorrhages which have been described could be explained on a similar basis.

In " post-infectious encephalomyelitis " vascular engorgement has been reported by most observers, thromboses by several, and perivascular hemorrhages by some. The presence of thrombi in post-measles " encephalitis " has received especial attention from Kreider [26] in Ferraro's laboratory.

It seemed worth while, therefore, to make a special review of the subject. This proved not as easy as had been anticipated. Aside from the difficulties of collecting material,* it was found that the ordinary routine stains and the usual neuropathologic methods were entirely inadequate for a study of thrombi and finer vascular changes. Finally, Masson's stain on paraffin material was tried, and appeared satisfactory. The results of the investigation will be published in detail elsewhere, and are merely summarized here.

In a case of post-vaccinal " encephalitis " and in another histologically similar case, but without known etiology, the vascular changes may be summarized as extreme engorgement, phagocytosis of brown pigment with and without perivascular hemorrhage and intravascular clot formation. In numerous vessels, large and small, there were masses of platelets, a heavy deposit of fibrin adherent to the walls and endothelial proliferation (figure 4).

In every one of 14 cases of multiple sclerosis in which material was available for adequate study, marked vascular changes were observed. The adventitial proliferation, doubtless a result of perivascular infiltration, has already been referred to. In addition, an engorgement, tortuosity and proliferation of veins in the vicinity of plaques were striking (figure 5).

* I am greatly obliged to my friends, Dr. George Hassin of Chicago, Dr. K. Loewenburg of Ann Arbor, Dr. Cyril Courville of Los Angeles, Dr. William Shapera of Pittsburgh, Dr. John Dwyer of Springfield, Mass., and Drs. S. B. Wolbach, T. Leary, F. Parker, C. S. Kubik and I. B. Akerson of this city for their kindness in supplying pathologic material.

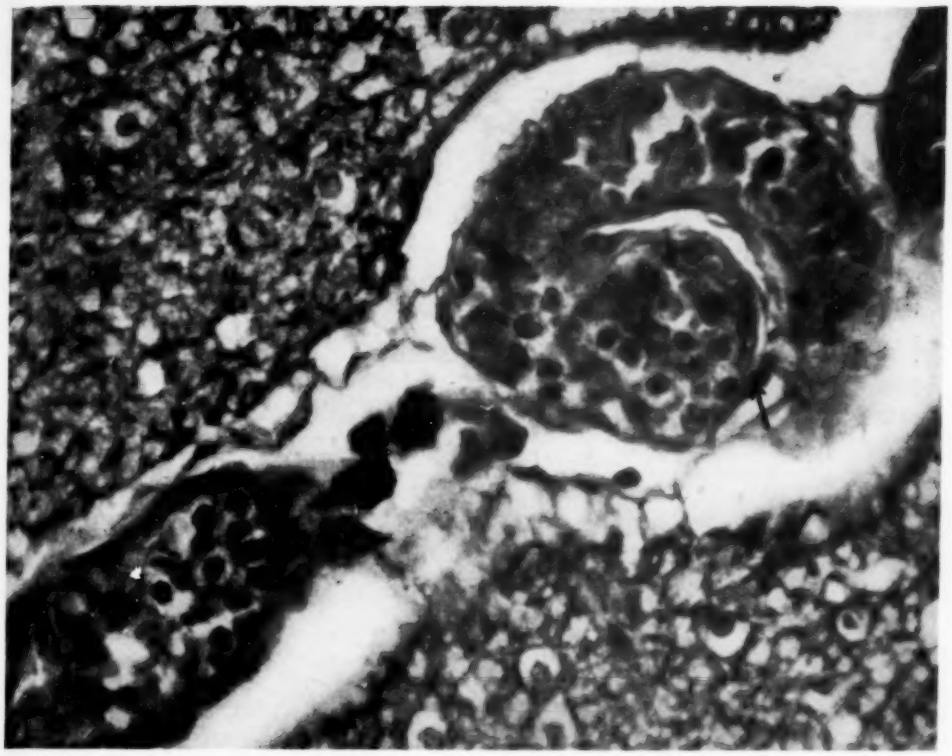


FIG. 4. Post-vaccinal "encephalitis." Engorged vessel, containing a mass of fibrin adherent to the walls and clumps of leukocytes. Cells are growing along a fibrin strand (arrow). Masson stain, oil immersion lens.

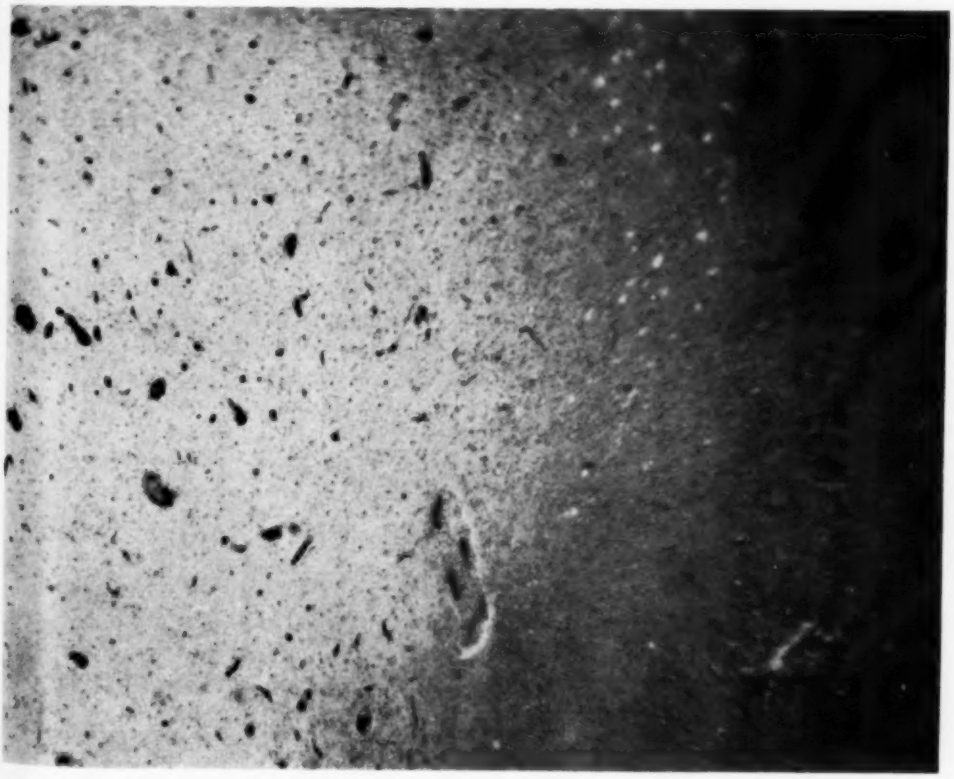


FIG. 5. Multiple sclerosis. Congestion and proliferation of vessels in a plaque (on left of photograph) in the cerebral white matter. Masson stain, low power.

Brown pigment was seen in endothelial and adventitial cells. Clots of fibrin and leukocytes occurred in vessels of various sizes, but they were less numerous and intense than in the cases of "encephalomyelitis." In some of them, invasion by endothelial cells could be demonstrated (figure 6). Complete occlusion of vessels by fibrous tissue was encountered with considerable frequency.

Can these changes be secondary to the parenchymal degeneration? A similar study was made of the vicinity of old softenings, which had produced massive secondary degenerations accompanied by dense gliosis. The vessels

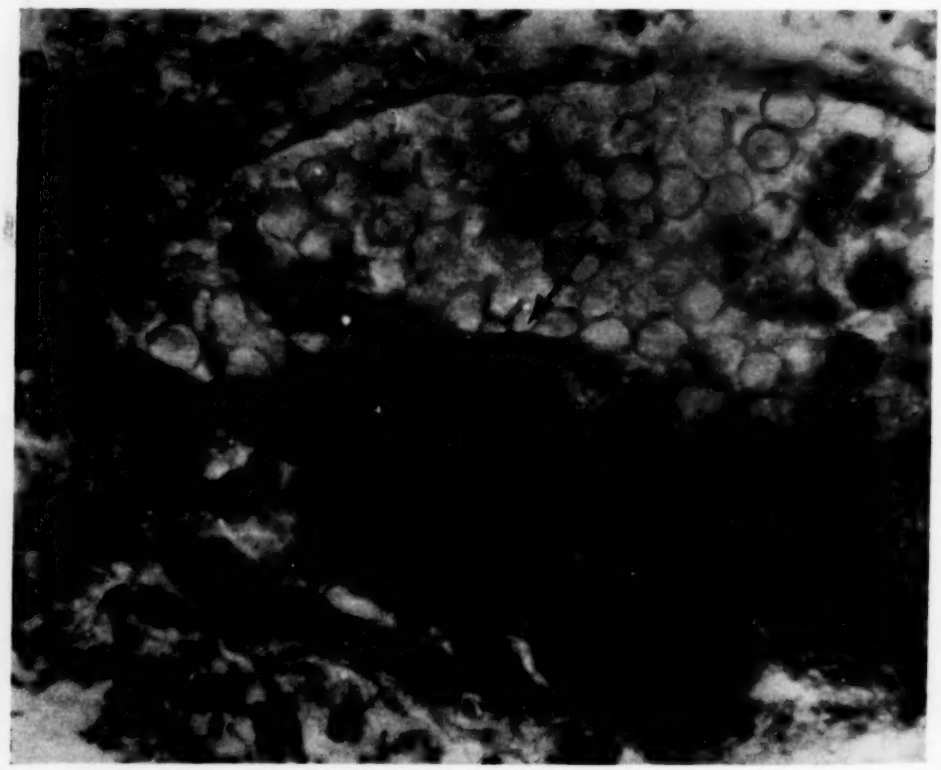


FIG. 6. Multiple sclerosis. Platelet clot adherent to wall of vessel, with fibroblast (arrow) growing over the surface. Masson stain, oil immersion lens.

in such areas were approximately normal in size and number, not engorged, their walls contained no pigment, and their lumens contained no clots. There was often a thickening of the adventitia, which occasionally still held a few phagocytic cells.

Since, therefore, the vascular obstructions and dilatations seen in multiple sclerosis and "encephalomyelitis" are not regularly encountered in other types of degeneration, and since demyelination may be produced experimentally by venous obstructions, it seems reasonable to conclude that the

thromboses are primary to the changes in the nervous tissues, and not secondary. The histologic details will be discussed more fully in a paper now in preparation.

The Part Played by Toxins and Other Exogenous Factors

It has often been pointed out that the exacerbations of multiple sclerosis are apt to follow infections of various sorts. Pregnancy, trauma, chilling, the injection of foreign protein, and severe emotional strains are also mentioned as precipitating attacks. Von Hoesslin,[27] who has recently reviewed the subject, finds that one or the other of the factors mentioned appeared to be associated with the onset or progression of the disease in a large proportion of the cases which he studied. He concludes that there is probably also a predisposition to multiple sclerosis which is perhaps inherited.

If the lesions of multiple sclerosis are the result of thrombosis, it appears natural to seek the predisposing factor in the coagulating mechanism of the blood. Brickner [28] has described an abnormal lipolytic activity in the serum of patients suffering from multiple sclerosis, and McKenna [29] has pointed out that a leukocytosis is frequently found. It is not obvious, however, just how such abnormalities have a bearing on the presumed occurrence of thromboses.

The matter appears clearer since Solomon and Simon [30] demonstrated a functional abnormality in the clotting time in a series of patients with multiple sclerosis. Injection of adrenalin or of typhoid vaccine caused a more marked and more prolonged decrease in clotting time (that is, *increase* in coagulability) than in normal controls or patients with other neurologic diseases.

The mechanism of this increased lability of blood coagulation is still under investigation. It has been found that the blood fibrinogen is high in the majority of cases of multiple sclerosis examined. The blood calcium is within normal limits. No constant abnormality has been demonstrated in the platelet count, but in some instances there appears to be an abnormality in the behavior of the platelets. It is possible that some of the tests may be of diagnostic value.

The results of these investigations may be taken, then, to support the suggestion that some fundamental disorder of the blood leads it to clot in the cerebral venules of the central nervous system as a result of stimuli, infections, pregnancy or emotional upsets which normally would lead only to a mild increase in coagulability.

Therapeutic Implications

No attempt has been made as yet to formulate a definite therapeutic program on the basis of the theory which has been outlined, but it is not difficult to visualize various methods which might be tried. It might be possible, for example, to lower the level of fibrinogen by diet, or to cause

a decrease in the number of platelets, or to administer a suitable anticoagulant drug. It seems wiser, however, first to define the fundamental abnormality more clearly, if only because of the extraordinary difficulty of reaching a true estimate of the results of treatment simply from symptomatic and neurologic changes.

Obviously, the presumed exciting factors should be avoided if possible. Infections, accidents, and emotional upsets are not easily circumvented, but female patients should be advised not to become pregnant.

Certain negative conclusions are evident. Little is to be hoped for from antiseptic treatment. Heat treatment and cervical sympathectomy can have scarcely more than temporary value, if any. Treatment by injection of foreign protein is certainly to be avoided.

Summary

1. The histologic features of the lesions of multiple sclerosis have been produced experimentally in animals in two ways: by the injection of minute doses of tetanus toxin, and by obstruction of cerebral venules.

2. Thrombi and obstructed vessels have been observed in the lesions of multiple sclerosis, and in those of "post-infectious encephalomyelitis," apparently an acute form of the same pathologic process.

3. It has been recognized, although rather vaguely, that there may be an association between the exacerbations of multiple sclerosis and infections, pregnancy and accidents.

4. Recent clinical investigations have shown that, although the clotting time is usually within normal limits in cases of multiple sclerosis, the coagulability of the blood is greatly increased by the administration of adrenalin or of typhoid vaccine, as compared with controls.

5. Therefore, there is probably a fundamental abnormality in the blood in multiple sclerosis, which interacts with endogenous or exogenous factors to cause thrombi in the cerebral venules.

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CORRELATIONS OF THE ENDOCRINE SYSTEM *

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UNTIL recent years, all discussions of the interrelations of the different endocrine glands were in effect discussions of a single simple diagram, which was introduced by Eppinger, Falta and Rudinger [1] as long ago as 1908, and which is still to be found in certain textbooks of physiology and of medicine at the present day. The diagram took the form of a triangle, whose apices represented the pancreas, the thyroid, and the adrenal medullae; between the two last-mentioned, a mutually synergistic relation was supposed to exist, while the two other sides of the triangle represented reciprocal inhibitory actions. It was not founded upon any very impressive assemblage of experimental data; it obviously left out of count members of the endocrine system whose importance is now more generally recognized; and it gave no explicit suggestion of the nature of the antagonisms and synergisms postulated.

From a purely theoretical standpoint, we may recognize that there are three entirely different mechanisms possible, each of which may lead to one hormone appearing to act as an antagonist to some other hormone. In the first place, the two hormones might react chemically with one another, as an acid reacts with an alkali, to their mutual destruction; so that chemically-equivalent amounts of the two hormones, administered together or secreted simultaneously, would exactly cancel out; with unequal mixtures, the physiological effect would be determined by the difference in the amounts of the two hormones, and could be calculated by subtraction.

In the second place, the two antagonistic hormones may act upon the same responsive tissue, but produce therein opposite or at least incompatible reactions. Arguing by analogy from the few instances that have received satisfactory study, by Clark,[2] Gaddum,[3] and others, we may regard it as probable that in such a case the physiological effect of combined action is to be calculated, not by subtraction, but by division; that is, that it depends, not on the difference, but on the ratio between the two substances.

There is yet a third possibility: one hormone may act upon the endocrine source of some other hormone, so as to inhibit its activity, and decrease the rate of secretion. This may also give rise to an apparent antagonism, which may be physiologically or clinically conspicuous but will tend to disappear in experiments of the pharmacological type in which both the active principles are introduced in known amounts. The action of any one hormone upon some other endocrine gland may be direct or indirect; it may take place by the mediation of the nervous system, or of some third endocrine gland whose participation in the process may easily escape notice.

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It is easy to see that these are three fundamentally different types of antagonism; and that there are three analogous and parallel different types of synergistic action, all theoretically possible. Diagrams such as that set up by Eppinger, Falta and Rudinger make no attempt to distinguish between these three possible types of antagonism, or of synergism; but today we are dissatisfied with such vague positions, since in many instances the nature of the observed antagonistic and synergistic effects has been more or less fully elucidated.

No examples of the first type of interaction between hormones have been established; and it does not at present seem probable that direct chemical reaction between different hormones occurs in the body. It was formerly usual to speak of the relation between the characteristic male and female sex hormones in such terms; but it is now clear that such a view is physiologically untenable and, at least for androsterone and the estrin group, chemically impossible.

The second type of interaction is well exemplified by the ovarian hormones: estrin, the follicular hormone, on the one hand, and the corpus luteum hormone, progestin, on the other. Both act upon the same group of responsive tissues, in the uterus, the vagina, and the mammary glands; in some cases, or in some circumstances, their actions are incompatible. The enormous difficulty of obtaining the characteristic vaginal response to estrin in the presence of an active corpus luteum is well known; and the suppression of the usual uterine responses to progestin (progestational proliferation, sensitization to trauma) by administration of estrin has been described many times. On the mammary gland, however, these two hormones have similar or complementary effects. Even in the case of a single tissue, the endometrium of the rodent uterus, the two hormones may be in some respects antagonistic and in others synergistic: this tissue, when sensitized by a relative excess of progestin, responds to certain types of trauma by the formation of a large mass of decidual cells, the deciduoma of Loeb [4]; this reaction can be prevented by the administration of estrin. A tumor-like mass of quite different, conspicuously hydropic character may develop, in response to the trauma of slitting in the presence of both estrin and progestin.[5] In the formation of this type of tumor, which has been called the endometrial mole, progestin appears to reinforce and enhance the action of estrin; whereas, in the formation of the deciduoma type of tumor, from the same tissue, estrin inhibits the action of progestin.

Endocrine interrelations of this type may be exceedingly complex. Thus the glycogen-storing cells of the liver are influenced by insulin, adrenalin, the thyroid hormone, probably the hormone of the adrenal cortex, and possibly a hormone of the anterior pituitary; nor are they indifferent to less specific changes in the composition of the blood supplying them, such as changes in hydrogen-ion concentration and sugar concentration. It is obvious that so tangled a skein is not easily unravelled; and that the effect upon the liver glycogen of treatment with an anterior pituitary extract

(which may have a direct action, but is likely also to affect the thyroid and the adrenal cortex and to act upon metabolism in various ways both direct and indirect) is not easily interpreted.

Such discussions lead naturally to a survey of the third type of endocrine correlation: the effects, stimulating or inhibitory, that a hormone may have upon some other endocrine gland. The most familiar, and undoubtedly most important instances are the dependence of the thyroid, the gonads, and the adrenals upon the anterior pituitary. It is well known that hypophysectomy leads to an almost complete cessation of activity, and to striking atrophic changes, in these dependent organs; and that these effects of hypophysectomy may be corrected, temporarily at least, by replacement therapy with suitable pituitary extracts. Moreover, the anterior lobe itself is affected by changes in the activity of these dependent organs, the gonads, the thyroid, and (probably) the adrenal cortex. It is certain that these reciprocal relationships between certain glands and the anterior pituitary play a predominant part in the correlation of the endocrine system; and they cannot be passed over thus briefly.

In the meantime, however, it is interesting to note that while the importance of these pituitary correlations is ever more widely appreciated and applied in interpretation, there are relatively few other instances of action of hormones upon endocrine glands. A number of supposed cases of this type of interrelation have been shown, by further study, to be indirect actions, or to be non-specific. Thus the fact that the normal rhythm of estrus is usually interrupted by destruction of the adrenal cortex does not indicate a direct action of the cortical hormone upon the ovaries, since it has been shown [6] that if the general condition of the adrenalectomized rat can be satisfactorily maintained by supplying large amounts of salt, the estrus cycles continue. The anestrus after adrenalectomy is therefore the reflection of a generalized cachexia and comparable to the anestrus of starvation; it is probable that the anestrus observed in experimental hyperthyroidism is, in part at least, of similar origin and not to be regarded as evidence of a specific action of the thyroid hormone upon the ovaries. There is some reason to believe, however, that the thyroid hormone has a direct influence upon the development of the islets of Langerhans,[7] and that the ovarian and testicular hormones cause atrophic involution of the thymus.[8]

In the above-mentioned instances the effect appears to be specific, and it is likely, though not certain, that it is direct. There are other cases in which specificity is not in question, but which must be regarded as indirect. The statement that administration of adequate doses of insulin leads to discharge of adrenalin is merely an abbreviated way of saying that the insulin usually produces a fall in blood sugar, which in turn stimulates the nervous centers controlling adrenalin secretion.[9]

Among these indirect correlations of this type, none are more interesting at the present day than those in which the anterior pituitary plays the mediating rôle. Before these can be discussed, it will be necessary to examine

more closely the direct linkages involving the anterior pituitary. The multiplicity of endocrine activities with which this minute gland has been credited has become almost a byword; and it is too true that some investigators, discovering some minor consequence of injections of pituitary extracts, have been uncritically rash in assuming a direct specific mechanism and postulating a new pituitary hormone. Nevertheless, the fractionation of pituitary extracts into partially-purified products has shown, by the manner in which the manifold activities of the crude original extract have been distributed among the final fractions, that the situation is extremely complex. This chemical dissection of the gland, though far from complete, already permits one to say with some degree of confidence that at least seven distinct and separable hormones are present in the crude extracts. Prolactin, which develops the crop-gland of the pigeon, and brings the developed mammary gland of the mammal into active secretion, possesses distinctive chemical properties which permit its separation from the other active principles.[10] Equally distinctive, though very different, are the properties of the adrenotropic hormone, assayed by its power to restore the atrophic adrenal cortex of the hypophysectomized rat.[11] It does not seem possible to doubt that there are two active principles affecting the ovary, one primarily follicle-stimulating and one promoting luteinization.[12, 13] The thyreotropic hormone, which causes hyperplastic changes in the thyroid gland and increased secretory activity in susceptible animals, may be separated from the foregoing.[14] The ketogenic principle, which in some unexplained but probably direct manner intervenes in metabolism to cause an accumulation of acetone bodies in the blood, is found to be distributed among various fractions in such a way that it cannot be identified with any of the other accepted hormones.[15] The growth hormone may be obtained reasonably free from the others.[16] Beyond this it does not, at present, seem profitable to go. It has already been hinted that the principles above mentioned can, in so many different ways, play a part in carbohydrate metabolism, that the existence of a specific hormone acting directly thereon is very hard to establish; if such a substance exists, it is hard to separate from the growth hormone. A dependence of the parathyroids upon the anterior pituitary seems rather clear in some species,[17, 18] but the evidence for a specific pituitary hormone with a direct action on the parathyroids[19] is relatively scanty. Other postulated pituitary hormones rest upon still more slender bases.

The importance of the anterior pituitary in endocrine correlations is only in part due to the fact that its hormones control other endocrine glands; it is also partly due to the fact that these glands reciprocally influence the anterior lobe. This aspect of the question has been studied in three somewhat different ways. In the first place, histological changes or gross changes in the anterior lobe may be noted after the ablation of some endocrine gland, or after the administration of some endocrine principle. The existence of an effect may be demonstrable in this way, but the nature of the effect remains somewhat obscure. When only two pituitary hormones—growth

and gonadotropic—were recognized, it was tempting to connect them with the two chief types of granulated cells in the anterior lobe, and to interpret histological changes accordingly; but if at least seven hormones are postulated, the interpretation can hardly be carried out in detail.

Secondly, the effect of various experimental procedures upon the amount of one or other of the hormones actually present in the anterior lobe may be approximately determined. The pituitaries of the experimental animals may be introduced, either as implants or as crude extracts, into suitably reactive test animals and the magnitude of the effects obtained noted. Such procedures are subject to the usual errors of the cruder methods of biological assay; and moreover the interpretation of the findings is fundamentally ambiguous. It is well known that the withdrawal of ovarian hormones by castration leads, in many species, to marked histological change and increase in size of the anterior pituitary; if the pituitaries of such castrates are implanted into immature female rats or mice, they prove to be unusually rich in gonad-stimulating principles; and there is ample additional evidence to show that the anterior lobe not merely contains large amounts of these substances, but that it secretes them in far larger quantities than usual. In this case the amount of hormone present in the anterior lobe is an index of its activity. This correlation is not inevitable. Thus it has been argued [20] that the anterior pituitary of the pregnant woman is deficient in gonadotropic hormones, not because it is not producing them, but rather because it is producing them so rapidly that they are not stored in the gland itself. Similarly the hyperactive thyroid gland in exophthalmic goiter contains less than the usual quantity of thyroxin.[21]

Thirdly, it is in some cases possible to obtain direct evidence of the degree of the activity of the anterior lobe. The amount of the hormone under consideration present in the circulating blood may be measured, and unless the rate of destruction or of excretion of the hormone varies greatly there will be no likelihood of errors in interpretation. Thus the hyperactivity of the pituitary of the castrated rodent has been established by cross-circulation (parabiosis) experiments [22] and by assays of samples of drawn blood.[23] Alternatively, structural or functional changes in the animal itself may be indicative of altered pituitary function: for example, the occurrence of thyroid hyperplasia after castration may be taken to mean that the anterior lobe has increased its production, not merely of gonadotropic substances, but also of thyreotropic hormone; an interpretation supported by the finding [24] that the thyreotropic-hormone content of the pituitary is increased.

This last example brings the discussion back to the point from which it started: namely, that the influence of one hormone upon some other endocrine gland may take place through the mediation of the anterior pituitary. There is no doubt that this is a common occurrence in experimental studies, and it is probable that it is of great physiological importance in the integration of the endocrine system. Examples are not far to seek: when the ad-

ministration of large doses of pregnancy-urine preparations stimulates the ovaries of the rat to unusual endocrine activity, there results an activation of the pituitary which in turn produces enlargement and hyperplasia of the thyroid [25]; again, enlargement of the adrenals seen after treatment with extremely large doses of the ovarian hormone estrin [26] is similarly ascribable to activation of the anterior lobe to produce the adrenotropic hormone. Evidence that the pituitary does participate in these reactions is furnished by the fact that in both instances enlargement of the anterior lobe occurs to a marked degree, and also by the fact that neither effect is obtainable in animals from which the pituitary has been removed.

On the whole, it does not seem that these reactions are highly specific. The structural changes in the anterior lobe produced by thyroidectomy are somewhat similar to, though distinguishable from those produced by ovariectomy; in both cases, the thyreotropic-hormone content of the gland is increased.[24, 27] One gains the impression that, as a general rule, the anterior lobe reacts with a generalized increase or decrease in activity to alterations in the supply of hormones from the dependent endocrine glands. If the pituitary secretes many hormones, it seems theoretically possible that it might secrete any one of them in excess and the rest in normal amounts; but it is hard to find cases in which this theoretical possibility seems to be realized in practice. Pathological hypersecretion of the growth hormone, producing acromegaly, is very often accompanied by signs of hypersecretion of thyreotropic hormone (causing elevation of the basal metabolic rate by thyroid stimulation), by symptoms of diabetes, and in some instances at least by signs of over-production of gonad-stimulating hormones. Yet this problem has not been thoroughly explored, and experimental means may yet be found whereby one of the manifold endocrine functions of the anterior pituitary may be influenced without disturbing the others.

Perhaps an instance may be found in the study of lactation. Since removal of the pituitary at any time during lactation promptly halts the secretion of milk,[28] it is clear that the pituitary hormone prolactin is supplied throughout the whole period; and it has been shown that the mechanical stimulation of the nipples during suckling is responsible for the maintenance of prolactin secretion.[29] In this case it does not seem that the anterior lobe is activated as a whole; the ovaries, for instance, are quiescent —if they are experimentally roused to activity, pituitary function is affected and milk secretion fails [30, 31]—and this might indicate that the anterior lobe, though actively producing prolactin, has ceased to secrete gonad-stimulating hormones. However, since it seems that prolactin itself has an inhibiting effect upon the ovaries,[32] it is not certain that the interpretation indicated is the correct one.

This example introduces into the question of endocrine correlations the factor, hitherto omitted, of nervous links in the chain of interrelations. It seems difficult to suppose that the influence of suckling upon the pituitary is

transmitted by other than nervous routes; yet since the more obvious possible nervous pathways may be interrupted without effect, it is hard to conceive what these routes may be.[30] The same difficulty arises in considering the sudden burst of pituitary activity which follows mechanical stimulation of the genital region in the estrous rabbit. Yet despite the difficulties, it is hard to escape the view that pituitary function is to some extent under nervous control, and is influenced by stimuli arising peripherally or originating in higher centers. It has even been suggested [33] that the effect of hormones such as estrin upon the pituitary is indirect, and involves the stimulation of a center controlling the anterior lobe by unidentified nerve fibers; but since this view is based chiefly on failure of the usual pituitary response to estrin in transplanted (hence denervated) pituitaries, and since this organ does not lend itself well to transplantation, the question may be regarded as still undecided.

This question of the nervous control of the anterior lobe is not more difficult than the problem of nervous regulation of other endocrine organs. The adrenal medulla furnishes an unique example of an endocrine gland whose activity is quite certainly dependent primarily upon its innervation. The theory that there are true secretory fibers to the cells of the pancreatic islets remains a highly controversial and difficult topic; the same might be said of the thyroid gland. On the whole, interest in the question of nervous correlation within the endocrine system has decreased with the increase in knowledge of hormonal correlating mechanisms and especially of the central part played by the anterior pituitary.

No discussion of endocrine correlations could now be complete without some mention of the "anti-hormones." These substances, of unknown nature and origin, appear in the circulation of animals subjected to prolonged treatment with certain pituitary extracts, and are detected by their power to inhibit the action of such extracts. Our knowledge of them has been summarized elsewhere,[34] and is not yet adequate to permit any evaluation of the part they play in the complex system of actions and reactions which ensures the integration and correlation of the endocrine system.

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ARTERIOSCLEROSIS AND HYPERTENSION IN DIABETES *

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That arteriosclerosis occurs in excessive degree in diabetic patients has found general acceptance among American students. The importance of characteristic metabolic changes of diabetes in its causation was pointed out in the first study of Deaconess Hospital autopsy data by Root and Warren.[1] Further reports by Joslin [2] emphasized the clinical significance of arteriosclerotic complications of diabetes, and Warren [3] summarized the pathologic data bearing upon arteriosclerosis in a large series of diabetics. Other aspects of this problem require investigation, such as (1) when does the excessive arteriosclerosis found in diabetic patients develop? (2) what are the characteristic steps in its progress? (3) are the morphologic changes of arteriosclerosis in diabetes different from those in non-diabetic patients? In this paper briefly are summarized the results of an analysis of the clinical records and the postmortem examinations of 175 diabetic patients at the New England Deaconess Hospital.

Fifty-four per cent of the cases had had hypertension indicated by a systolic pressure exceeding 150 millimeters of mercury. A few patients were included who had only a single blood pressure reading between 150 and 160 millimeters. A considerable number of the hypertensive group could not be said to have a constantly elevated blood pressure. Little attention was paid to the diastolic pressure although it varied from 80 to 130 in the hypertensive group and, though its more fundamental importance is conceded, no great change in the classification of the patients would have occurred by using the diastolic pressure.

The 175 cases included 100 females and 75 males, of whom 93 had a systolic blood pressure at some time between 150 and 230 mm. mercury. Obesity had been present in 87 per cent of the hypertensive and 74 of the non-hypertensive group. The average age at death was 63 years for the hypertensive group and 51.1 for the non-hypertensive group. All the children and cases under 30 years of age fell in the non-hypertensive group.

Age at Onset of Diabetes. The old concept of diabetes as a degenerative disease of old age received its death blow from the publication of data by Pincus, Joslin and White [4] based on 9853 cases of true diabetes. They showed clearly that the frequency of onset of diabetes declined after the sixth decade. The rate for frequency of onset indicates the susceptibility to the development of diabetes, and it is clearly evident from their data that

* Read at the Philadelphia meeting of the American College of Physicians, May 3, 1935.
From the George F. Baker Clinic, Elliott P. Joslin, Medical Director, New England Deaconess Hospital, Boston, Massachusetts.

diabetes is not a disease produced by senility. Actually the susceptibility to diabetes in the eighth decade of life is less than in the third decade. If vascular disease was a significant factor in producing diabetes, how would we explain the fact that 10 per cent of all diabetes begins in the first 15 years of life, and two-fifths before the fortieth year? In this series, 21 per cent of the cases among males and 17 per cent among females began before the age of 30 years. Furthermore, errors are all in the direction of postponing the age at onset. Eighteen cases died under the age of 40 years; of these, seven had had diabetes over five years, and every one had arteriosclerosis, including two boys 16 years of age, and Case No. 1794 that died at 33 years of age with coronary occlusion. None of these cases under the age of 40 years had hypertension.

Development of Excessive Arteriosclerosis. For a demonstration of the difference in the extent and severity of arteriosclerosis in diabetes as compared with non-diabetics, a series of 170 non-diabetic autopsies examined at the New England Deaconess Hospital by the same pathologist was compared with this series of 175 diabetics (see tables 1 and 2). The 170 cases

TABLE I

Coronary Sclerosis in 175 Diabetics at Autopsy

Cases	93 Cases with Hypertension			82 Cases without Hypertension		
	Absent	Slight to Moderate	Advanced	Absent	Slight to Moderate	Advanced
Per cent	7.5	32	60	44	34	22
Age, yrs.	61	61	63	43	57	57
Duration of diabetes, yrs.	3	7	11	4	6	8

Note: "Advanced" means marked obliteration of lumen and includes cases with old and recent gross infarction.

TABLE II

Coronary Sclerosis in 170 Non-Diabetics

Cases	Absent	Slight to Moderate	Advanced
Per cent	37	50	13
Age, yrs.	58	64	66

were unselected except that no cases under 40 years of age were included, whereas in the diabetic group some 18 cases died under the age of 40 years. This difference would have the effect of handicapping the diabetic group since the older non-diabetic group would have more ordinary arteriosclerosis consistent with age. Without quoting in detail any percentages, a striking

excess of advanced arteriosclerotic lesions occurred in the diabetics. Thus, advanced coronary sclerosis with occlusion occurred in 40 per cent of the diabetics and in only 13 per cent of the non-diabetics, in spite of the fact that the diabetics averaged six years younger than the non-diabetics. Our first problem, then, was to determine whether this excessive arteriosclerosis was present when the diabetes began or whether it could be shown to have probably occurred after the onset of diabetes.

For this purpose we selected only those cases of diabetes with duration of one year or less on the assumption that diabetes of such short duration could not have produced much change in the arterial system. There were 23 such cases and in table 3 are shown the average figures. It will be seen

TABLE III

Aortic Atherosclerosis in 23 Diabetics and 170 Non-Diabetics at Autopsy

Grade of Sclerosis	Diabetes Less Than One Year in Duration		Non-Diabetics	
	Number	Per Cent	Number	Per Cent
Slight	14	61	94	55
Moderate and Advanced	9	39	76	45

that in the 23 cases, although their average age was not materially different from that of the non-diabetics, the frequency of severe arteriosclerosis in the aorta was somewhat less than in the non-diabetics. Similar results were obtained when the coronary vessels were compared. If now, cases with diabetes of long duration are examined, the contrast is striking.

Duration of Diabetes. In 46 cases the duration of diabetes exceeded 10 years, the youngest case at death being 43 years of age with diabetes of 15.1 years' duration. The oldest case was 83 years with diabetes for 33 years. In 32 of the 46 cases hypertension had been present. Twenty-five of these 30 cases died as a result of coronary occlusion. Thus, in this group with diabetes of long duration coronary disease as the cause of death was just four times as frequent in the diabetics as in the non-diabetic control series.

Frequency of Hypertension. The excessive frequency of hypertension in diabetic patients has been a matter of frequent comment. Bell and Clawson [5] from necropsy statistics showed that 42.5 per cent of diabetics had hypertension, and they regarded hypertension as 2.7 times as frequent in diabetics as in non-diabetics. Major [6] also regarded hypertension as more frequent in diabetes. Unfortunately it is difficult to state the relative period of onset of hypertension and diabetes in most series of cases with accuracy. In this series where accurate data were possible, it is true that diabetes preceded hypertension in the majority of cases. Recently in a review of 482 cases under observation for 10 years the blood pressure rose from normal to a level above 150 mm. mercury in 16 per cent of the cases, and in 50 per cent rose over 10 mm. of mercury.

Localization and Type of Vascular Change. Aortic atherosclerosis was excessive in the diabetics in this series, in contrast with the 170 controls and in contrast with the aortic lesions in 5060 consecutive post mortems reported by Willius et al.[7] Absence of atherosclerosis of the aorta occurred in only 7 of the 175 diabetics, and their average age was 26 years and the duration of their diabetes only 0.9 year. The difference in degree of severity is indicated by the frequency of Grade IV lesions. In Willius' series 49 such cases occurred in the 3473 over 40 years of age, or 1.4 per cent. Among our diabetics Grade IV lesions, that is with calcification and ulceration, occurred in 37 cases or 21 per cent, an incidence 15 times as great. Advanced lesions in the diabetics occurred eight times as frequently in the hypertensive as in the non-hypertensive diabetics.

Chemical differences in the aortae of diabetics and non-diabetics studied at the Deaconess Hospital were found by Lehnherr.[8] The cholesterol content was 8.07 grams per cent in the diabetics as compared with 4.8 grams per cent in the non-diabetics. In the adult diabetic cases the average calcium content was 5.2 grams per cent as compared with 1.57 grams per cent for non-diabetics. There seemed to be a definitely increasing percentage of fatty acids with increasing atherosclerosis, although certain cases presented exceptions. The source of the lipids which appeared in the aortae is not revealed. Whether they come from the blood stream or are formed from chemical disintegration of substances in the wall of the vessels remains unproved.

Heart Disease. Coronary sclerosis with the changes secondary to occlusion, either acute or chronic, was the characteristic finding in the diabetics. In the first table these findings are summarized as follows:

Coronary sclerosis was absent only in those cases where the average duration of diabetes was three years. Advanced coronary sclerosis, including only cases with occlusion of the coronary arteries, occurred in 60 per cent of 93 cases with hypertension and 22 per cent of 82 cases without hypertension, in contrast to only 13 per cent of the non-diabetic patients. The effect of duration of diabetes comes out clearly here because advanced coronary disease was twice as frequent in the diabetics as in the non-diabetics. The exceeding frequency of coronary disease in the hypertensive cases is in part related to the greater duration of diabetes and to their greater age. The striking feature of the diabetic heart is the lack of great hypertrophy except in those cases with preëxisting hypertension. This failure of hypertrophy may be due to the type of pathologic change found at autopsy, and is in marked contrast to the heart of myocardial insufficiency cases associated with essential hypertension; it suggests further that the hypertension may have followed the arteriosclerotic process, accounting thus for the limitation of any constant or marked hypertrophy.

Retinal Arteriosclerosis. During the present year two important reports on the eyes of diabetics have appeared, the one from the Mayo Clinic, Wagener, Dry and Wilder,[9] and the other reporting the examinations of

2000 diabetic patients at the Deaconess Hospital by Waite and Beetham.[10] Both papers come to one conclusion which completely reverses the previous conceptions of retinal arteriosclerosis and its relationship to the retinal disease seen in diabetes. Waite and Beetham at the Deaconess Hospital found that retinal arteriosclerosis is no more common among the diabetics than among a control series which they examined with equal care. The striking difference is in the frequency of retinal hemorrhages which increase steadily with the duration of diabetes and were unrelated to blood pressure or to retinal arteriosclerosis. Interestingly enough the same conclusion was arrived at independently by Wagener and Wilder who reversed their formerly expressed opinion upon this important subject. It, therefore, appears clear that these two papers bring out a fundamental point of divergence. Retinal hemorrhages are the characteristic feature of diabetes and are due to some specific metabolic effect exerted upon the capillaries. As a result extravasations of blood occur. These may be absorbed or may be organized. The waxy exudates seen may be due to hyaline degeneration of these hemorrhages. At any rate there is a great tendency in diabetes for fibrosis to occur with organization of the hemorrhages leading to retinitis proliferans. Edema of the discs and the changes characteristic of typical malignant hypertension were not observed in any of the diabetics at the Deaconess Hospital.

Peripheral Gangrene. Gangrene of an extremity had occurred in 48 of the 175 autopsies. In this group 32 patients had had hypertension in contrast to 16 with normal blood pressure. The striking feature, however, of the arteries in the leg is the similarity in pathologic findings in both the hypertensive and non-hypertensive cases. Diabetic gangrene is characteristically moist where senile gangrene is dry, owing to the fact that the changes produced by diabetes are primarily intimal and progressively occlusive in type. So-called Mönckeberg's sclerosis is a common type of sclerosis in the muscular arteries of the legs present in a considerable percentage of individuals after 50 years. Therefore it is to be expected that the diabetic legs at pathologic examination will show medial sclerosis; but the striking difference between the diabetic and the non-diabetic is not in the media but in the degree of intimal change. Here the marked localized proliferation of the intima with deposition of fatty material including cholesterol crystals is striking. This process goes on slowly with gradual encroachment upon the lumen, until trauma with infection, producing swelling and closure of the small arterioles or spontaneous thrombosis, leads to gangrene. In the small arterioles, obliterative endarteritis with hyaline thickening of the intima and obliteration of the lumen is the rule. Hypertension seems to serve as an additional burden accentuating the process. The important point is that the muscular type of arteries shows the changes produced by diabetes most characteristically.

Nephrosclerosis. An attempt was made to classify the degree of arteriosclerosis present in the various types of vessels in the kidneys in relation to

hypertension. It appeared that slight degrees of sclerosis were almost constantly found in the larger vessels and arterioles in the non-hypertensive group. The more advanced sclerotic changes in the larger vessels and in the arterioles, however, were more frequent in the hypertensive group. Hyalinization of the glomeruli was found about 1.5 times as frequently in the hypertensive as in the non-hypertensive group. Fibrosis of the glomeruli was reported almost three times as frequently in the hypertensive as in the non-hypertensive group. Intimal changes as noted elsewhere were most frequently found in the larger vessels. Cases classified as moderate to marked renal arteriosclerosis exhibited advanced vascular lesions elsewhere including coronary thrombosis, peripheral gangrene, cerebral thrombosis and hemorrhage, and all but one case showed marked to extreme aortic atherosclerosis with calcification. No case in our series died primarily of uremia, despite occasionally advanced degrees of nephrosclerosis. Renal insufficiency, when it occurred, was secondary to cardiac failure.

Pancreas and Spleen. The vessels of the pancreatic-splenic circuit revealed less constant and less easily interpreted findings. The control series studied by Warren [3] showed as high an incidence of pancreatic arteriosclerosis as the diabetics. Since then 83 cases have been added to the autopsy series at the Deaconess Hospital and in only 9.5 per cent of these was any serious pancreatic arteriosclerosis recorded. Hyalinization of the islands of Langerhans occurred independently of arteriosclerosis and was associated with the relatively mild type of diabetes. The frequency with which arteriolar sclerosis of the pancreatic vessels is observed in essential or malignant hypertension would lead one to expect a relatively high incidence of diabetes in these cases. This is not substantiated by autopsy reports of hypertensive cases. Bell and Clawson [5] state that only 5.5 per cent of the hypertensive cases over 50 years of age have diabetes. Murphy [11] in his series of autopsies of cases of hypertension found arteriosclerosis in the pancreas to parallel uniformly that in the kidneys. In a personal communication Murphy states that only 14 out of 352 cases had diabetes. This, in view of the age of the patients, he considered a low incidence. No good evidence exists for believing that arteriosclerosis of the pancreas plays any considerable part in the causation of diabetes.

In the spleen arteriosclerosis was present in 32 per cent of the hypertensive cases and in 26 per cent of the non-hypertensive cases. Arteriolosclerosis was present in 31 per cent in the hypertensive group and 31 per cent in the non-hypertensive group. The somewhat greater frequency of this condition in the splenic vessels in hypertension was not marked. Conclusions drawn from the occurrence of vascular sclerosis of splenic vessels are of doubtful value.

Discussion. Although our chief purpose is to present facts regarding the arteriosclerotic lesions in diabetes, contrasting the hypertensive and non-hypertensive cases, some discussion of their theoretical bearings may be permitted. First is the excess of arteriosclerosis in the coronaries, aorta and

legs in these diabetics as compared with control series of non-diabetics. Second is the fact that among 175 diabetics followed to death hypertension occurred in 54 per cent. Third is the occurrence of all the characteristic vascular lesions of diabetes (retinal hemorrhages, coronary occlusion, gangrene) in diabetics without hypertension as well as in cases with hypertension. The existence of hypertension cannot be considered a sine qua non of these complications. Fourth, the incidence of these vascular complications was greater in the hypertensive group, as if hypertension acted as an additional factor increasing greatly the tendency to such lesions. This conclusion must be qualified by consideration of the greater average age of the hypertensive group. The common observation in a diabetic clinic of hypertension developing as time goes by in cases previously non-hypertensive is not to be dismissed too readily as due merely to the natural incidence with increasing age. Fifth, the association of large vessel arteriosclerosis constantly whenever arteriosclerosis was present suggested that changes in the large arteries occurred first.

In considering the etiology of arterial hypertension it has become customary to divide the possible agents under five heads: (1) circulating substances, including hormones; (2) the influence of the nervous system; (3) the structural changes in the vascular system; (4) infections and allergy; (5) constitutional factors. For careful reviews the articles of Meakins, Durig and Weiss may best be consulted. The rôle of the nervous system in the regulation of blood pressure is outstanding. The sympathetic vasomotor system with its constrictive influence is counterbalanced by the activity of the parasympathetic vasomotor nervous system particularly through depressive reflexes. An increase in the pressor mechanism or hypoactivity of the depressor reflexes has been offered as a cause. There is no clear evidence in our cases of unusual psychic or nervous make-up on which to base the theory that hypertension occurred first and vascular disease followed. Similarly the rôles of infections and allergy lack support. It is true that in diabetes, infections of the kidneys are common and that hypertension may follow such infections. Somewhat more reasonable is the theory that the spotty lesions of arteriosclerosis represent the results of low-grade and repeated bacterial invasion or degeneration due to bacterial toxins. However, no one holds the larger arteries responsible for hypertension. One would have to assume that the infections cause a different reaction in the smaller arterioles.

The rôle of inherited constitution has been emphasized in relation to hypertension. Although nervous and psychic factors, vascular changes of senescence, infections and toxins contribute, they seem to be most effective in certain individuals who may have inherited certain anatomical and functional characteristics of the nervous and vascular systems. O'Hare, Walker and Vickers [12] obtained a history of vascular disease in 68 per cent of a group of patients with arterial hypertension. Weitz [13] concluded that hypertension is inherited as a dominant characteristic. On the negative side Benedict and Root [14] studied a man 92 years of age who showed little evi-

dence of arteriosclerosis and a normal blood pressure. His family history contained no deaths from vascular disease before the age of 75 years. That the predisposition to diabetes is inherited as a Mendelian recessive characteristic has received support from the studies of Pincus and White.[15] Possibly a tendency to vascular disease is also inherited in the diabetic, but it is significant that excessive arteriosclerosis only occurred after the onset of diabetes in our series.

The influence of circulating metabolites in the blood and anatomic changes in the vessels themselves can hardly be separated. So far as arterial hypertension is concerned, the rôles of glucose, salt, guanidine, the potassium-calcium ratio and of peptones in the blood are still not clearly defined. The effects of circulating hormones from the pituitary and adrenals, while definite, do not seem to explain more than a small portion of the cases. Other substances, such as cholin and cholin compound, histamine and pancreatic extracts, such as "padutin," have temporary effects upon blood pressure. The one substance found both in the blood and in the blood vessel walls with which, experimentally, typical atherosclerotic lesions can be produced is cholesterol. It is sometimes found in increased amounts in cases of hypertension. Durig points out that it is not the height of the cholesterol in the blood, but the degree of saturation which is important. In hypertension the serum is often over saturated with cholesterol even though concentration in milligrams per 100 c.c. is normal. Thus it is the relation between the cholesterol and the colloids of the serum together with the affinity of the cells of the arterial wall for cholesterol which determines the deposition.

Alvarez and Neuschlosz [16] believe that the arterial wall with marked absorption of cholesterol has a higher contractibility and the muscles of the arterial wall are thus sensitized to adrenalin. However, medial hypertrophy, such as would be expected with continued adrenalin stimulation, was not found in this series. The structural change in the walls of both arteries and arterioles in our diabetics is the outstanding feature. The changes in the younger cases, with relatively shorter duration of diabetes, are found in the aorta and larger arteries. Hypertension develops with increased resistance of the arteriolar bed caused by a narrowed arteriolar system. Arteriolar disease never occurred without advanced changes in the larger vessels as well. That increased arteriolar resistance is due to cellular and structural change rather than to spasm from nervous origin seems most reasonable.

Leary [17] has compared experimental atherosclerosis in rabbits with human coronary atherosclerosis. He points out that atherosclerosis forms 90 per cent of the important arteriosclerosis in human beings and that the coronary arteries, because they are of relatively simple structure, muscular in type and poor in elastica, afford the best field for observation of the process. The coronary arteries possess a buffer layer of muscle and cellular subendothelial fibrous tissue which differ from other muscular arteries. It is without a circulation of its own and depends upon imbibition. These arteries, be-

cause of their anatomical relationship, are subject to great strain, meeting high pressure from the blood-filled aorta and resistance from their compressed intramural branches which are closed during the muscular systole of the heart. Relatively they might be compared with the muscular arteries of the legs of diabetic patients which have been subjected to unusual strain because of the almost universal obesity of most diabetic patients. Leary finds that the characteristic lesion induced with atherosclerosis of coronary vessels is fibrosis associated with the presence of lipoid cells. In older age periods there are large accumulations of lipoid cells with very little accompanying connective tissue. As a result of poor nutrition massive necrosis occurs causing the so-called "abscesses." In the young adults, therefore, the standard cause of death is thrombosis following subendothelial necrosis. On the other hand, in the older group a rupture of the abscess occurs in the lumen of the artery followed by thrombosis. The process is primary in the intima. Lesions in the elastica and media occur secondarily.

Leary was able to reproduce the lesions accurately by the feeding of cholesterol to rabbits, and he points out that such lesions do not occur spontaneously in rabbits. The lesions produced varied in different animals in their extent and severity. This variation was comparable to the differences exhibited by human beings. In fact, he could produce all the stages of human atherosclerosis in the coronary arteries in the rabbit. He points out that eggs and milk, the most common sources of cholesterol, are really intended as foods for the infant or embryo. Man is the only animal that eats both eggs and milk throughout his lifetime and is the only animal that dies in early life from coronary sclerosis. He emphasizes the analogy with diabetes. Sugar is soluble and combustible, whereas cholesterol is not combustible, is difficult to excrete and tends to be stored. Various idiosyncrasies to cholesterol exist. An inherited poor metabolism of cholesterol is associated with an early death from coronary sclerosis. In diabetes with advancing age there develops an inefficiency of the cholesterol metabolism and more advanced arterial disease.

Our own view is that the premature and excessive development of vascular disease occurs predominantly in muscular arteries under the greatest physical strain, especially in obese patients, and is due to the metabolic changes of diabetes. The coronary and leg arteries are chiefly involved although changes in the arterioles are also found. The necessity of insulin in the glycogen metabolism of muscle and especially for the completion of the lactic acid cycle must be of some significance in this connection although the details are as yet undemonstrated. The importance of the disordered lipid metabolism, more easily demonstrated by present chemical and pathologic methods, is better understood. Hypertension then is an important contributing factor in the clinical course of the disease because it imposes additional strain, even when the patient has lost his obesity, and accentuates greatly the vascular changes in coronary and leg arteries. A further suggestion as to the metabolic factor in the arteriosclerosis of diabetes is the

fact that with modern treatment with insulin and diet more normally balanced, the frequency of arteriosclerosis in the legs of diabetic children is diminishing. The objective in the future should be the earlier possible diagnosis of diabetes and its more aggressive treatment. The final explanation will take full cognizance of the interrelationship of the endocrine glands, of the parts played by preëxistent obesity, by infections, especially of the kidneys, and by inheritance.

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THE PRESENT STATUS OF THE PROBLEM OF "RHEUMATISM" AND ARTHRITIS; REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1934 *

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* This report constitutes the second "Rheumatism Review" prepared at the request of the American Committee for the Control of Rheumatism. The editorial comments express the opinion not of the American Committee but of the authors, a subcommittee, of which Dr. Hench is chairman. The first review covered the American and English literature on rheumatic diseases for 1932 and 1933, and appeared in the ANNALS OF INTERNAL MEDICINE last year.

In the last century the patient who had articular disease presented no very complicated problem to his physician. The patient's whole body was probably not examined; his joints may or may not have been. But the diagnosis was easy. His story told the tale: he simply had "rheumatism." The treatment was equally simple—salicylates.[1] The current equivalent of salicylates was likewise probably prescribed to the man of the Old Stone Age whose arthritic fossil is now a museum piece, or to the patient who had arthritis deformans and whose case is described in a medical papyrus written in Thebes about 1550 B.C.[2]

The problem of "rheumatism" began to be complicated only when it became the subject of the intensive researches of the past few decades. The complexity of the situation is, unfortunately, not simplified by the international appearance, at too frequent intervals, of new classifications for rheumatic diseases—classifications too often the "arbeit" of one who feels that only thereby can he attain recognition as a specialist for rheumatism. Through the multiplicity of suggested nomenclatures and the profusion of publications on all phases of the problem, however, definite progress is discernible. By continued international study and coöperation the complicated problem will eventually regain, indeed is now regaining, a certain simplicity of a more enlightened type. As van Breeman, Secretary of the Ligue Internationale Contre le Rhumatisme, expressed it, the problem of rheumatism is a diamond with many facets. He who views it through only one facet will gain a totally different impression of its nature than will he who regards it exclusively from another angle. But he who will view it through many facets, and see it whole, will find the complicated becoming simple again. For after all, in the last analysis the diamond has the simple formula of carbon.

General Incidence and Occupational Distribution

The incidence of rheumatic diseases is apparently increasing. This is in part attributable to the fact that more individuals are living to the ages when chronic rheumatism is most prevalent. The survey by Bigelow and Lombard revealed that in the State of Massachusetts, of the total population more than 40 years of age one person in every 10 had "rheumatism." Eighty-three per cent of all patients who had chronic rheumatism, using the term in its broad sense, were between the ages of 40 and 80 years. After the age of 40 years the disease increased with each decade, so that of persons between 70 and 80 years of age, one out of every four was notably afflicted thereby.[2]

[These statistics pertain to those who actually complain of the disease. The roentgenographic and pathologic studies of others (Garvin, 1927; Keefer and Myers, 1933; Bauer and Bennett, 1933) revealed that actually from 90 to 100 per cent of all persons more than 45 years of age have some type of articular disease, chiefly of the degenerative (senescent, hypertrophic, osteo-arthritic) type which, however, according to Keefer and Myers is symptomatic in only about 7 per cent of cases.—Ed.]

In the State of Connecticut (population 1,655,000) about 50,000 people have chronic rheumatism, of whom about 2,000 are probably completely disabled thereby, confined to bed or chair, needing the constant care of others. So Lombard [2] has estimated, if the percentage incidence in Connecticut is equal to that in Massachusetts. The disease is 12 times as prevalent as cancer but only one-fortieth as fatal. Were death the end result, everyone would fear it more. Regardless of its relatively low mortality it must be taken seriously. Any disease which carries a 10 per cent morbidity among persons who have passed the age of 40 years warrants the greatest attention.

Invalidism from rheumatic diseases is increasing in Sweden also. Edstrom [3] studied its incidence among 3,500 communal workers of Gothenburg between the years of 1928 and 1932. Rheumatism accounted for about 12 per cent of all disability from sickness in this group. Comparing figures for 1932 with those for 1922, it appears that the amount of invalidism has about doubled in 10 years.

Why is it that one person falls a victim to rheumatism while another escapes? To some extent the answer may be found in studies on its incidence in certain occupations. Edstrom found rheumatic disorders much more frequently among outdoor workers (policemen and workers on trains and roads and in harbors and shipyards) than among those working indoors, as in factories.

[These statistics approximate those of Danischevsky, of Kahlmeter, and of Templaar and van Breeman.[4]—Ed.]

Of three major factors—infection, constitution, and external conditions—which determine the course in a case of chronic rheumatism, Edstrom expressed the belief that the components of the latter factor (housing and working conditions, climate, environment) are most important. Were an acutely affected person able from the onset of his illness to be placed under good hygienic circumstances, the disease might often be prevented from becoming chronic. Poor housing conditions and exposure to the vicissitudes of weather may be more important etiologic factors than infection, and more worthy of correction.

Rheumatism is more prevalent in rural than in urban communities, according to the Massachusetts survey.[2] Among persons whose economic status was poor the incidence was nearly twice as high as that among the well-to-do. More of those living in damp houses, than others, had the disease. It is probable that the relationship between poverty and rheumatism is attributable to environmental influences. The poor are unable to have as good a diet as the wealthy. They cannot afford good dentistry or early eradication of foci of infection. They are less protected from fatigue and malnutrition, from endocrine deficiency and from faulty digestion and excretion, chief predisposing causes of the disease. In Massachusetts four-fifths of the poor and about half of the well-to-do patients were not under the care of physicians.

The Factor of Predisposition. To some, data of the type just noted seem devoid of real value. Thus, Climie [5] has expressed the opinion that the masses of statistics relating to climate, housing, geographic soil, nourishment of the patient, and so forth, do not lead anywhere. The patient himself is lost sight of; a study of his internal milieu is more important than one of his external environment. What of the patient's own soil? Is there, in truth, a rheumatic diathesis, a fundamental inherent peculiarity of the person who will have rheumatism " which, granted the right coincidence of circumstances, evidences itself by that individual suffering an attack of rheumatism, the degree of illness or extent of body tissue involved depending (only) partly on the activating agent and partly on the state of preparedness of the individual, or in other words, upon his mental and physical condition at the time of the attack? " Adamson [6] agreed that study of the soil of the person who will have rheumatism or of the victim is an inquiry long overdue: " Much stress has been laid on the nature of the rheumatic attack; perhaps not enough on the resistance of the individual and his tissues. Let us (hereafter) regard the state of the infected tissues even more than the nature of the infective agent."

[Although studies on the patient's soil are being properly demanded with increasing frequency, investigators are slow to accept the challenge. Studies on the physiology of normal joints and on the immunologic and physicochemical status of normal persons, as well as those of rheumatic and " pre-rheumatic " individuals, are meager. To a large extent they await advances in knowledge of general immunity and development of new methods for demonstration of alterations therein. The few current reports on the chemistry and cytology of blood and tissues which are available are reviewed later in this article.—Ed.]

Classification of Diseases of Joints and Related Structures

Discussions of the various rheumatic diseases—those of joints and related structures—are arranged as in last year's review.[4] The scheme of classification is repeated: (1) those attributable to trauma; (2) those attributable to infections of known type; (3) those possibly, or probably, attributable to infection or related toxins; for example, rheumatic fever, atrophic (infectious, proliferative, rheumatoid) arthritis; (4) those of which the chief characteristic is degenerative change in tissue; for example, hypertrophic (senescent, degenerative, osteo-) arthritis; (5) those of which the chief, or only obvious characteristic is some recognizable, or suspected, chemical derangement—a none too well defined group which includes forms of arthritis commonly called " chemical," " metabolic," " allergic," " endocrine," and (6) a miscellaneous group of unclassifiable types. Fuller details and criticism of such a classification will not be repeated. The reader is referred to the first review.[4]

Diseases of Joints Related to Trauma

Etiologic and Clinical Considerations. Traumatic arthritis may result from acute (exogenous, extrinsic) trauma, such as that from falls, blows,

accidents, or from chronic trauma incident to the abnormal use of joints in connection with occupation, recreation, obesity or poor posture. In the former variety symptoms arise, as a rule, rather suddenly. In the latter type, in which endogenous or intrinsic trauma is operating, symptoms may develop so slowly that their connection with chronic trauma may be overlooked. O'Connor's [7] experience is that of others, that in such cases articular lesions may be well advanced without symptoms being noted until some unusual strain is superimposed on changes already present.

An acute injury to any articular component may be followed by minor symptoms and complete healing or by the production of traumatic arthritis with chronic disability. In two cases observed by Key,[8] contusions of articular cartilage led first to acute, then to chronic, monarticular, progressive arthritis unrelieved by conservative treatment. Because of continued pain and stiffness Key explored the knees. In each case a single, small, irregularly rounded mass of fibrillating, degenerating, necrotic cartilage was found. Synovial proliferation and villus formation were present, also several small, compact collections of round cells.

[These collections, seen in Key's photographs, seem to resemble those which Allison and Ghormley, 1931, considered specific for atrophic arthritis. Recently Fisher (1935) expressed the opinion that the lymphocytic collections of Allison and Ghormley were similar to those found by him (1929) in a minority of cases of atrophic arthritis. It should be noted that Fisher now speaks of those he described as perivascular. Those noted by Allison and Ghormley were not perivascular. Recent unpublished studies of Ghormley and Deacon strengthen their opinion of the specificity of non-perivascular round-cell collections for atrophic arthritis.—Ed.]

There are, according to Jepson,[9] four classes of traumatic backache: (1) when trauma affects a patient who already has arthritis of spine or pelvis, (2) when trauma affects only soft parts of the back, such as muscles, tendons, and ligaments, (3) when patients, because of faulty posture, have a predisposition to injury, and (4) when patients are affected by occupational strain. In Jepson's 50 cases of traumatic backache, injuries to the lumbar portion of the spinal column were most common; to the cervical portion, less frequent, and to the thoracic portion, which is the least flexible and least liable to injury, infrequent. Jepson reviewed the technic and significance of various tests used to localize injury or disease of the spinal column or pelvis and to distinguish between real and fictitious pain: Smith-Peterson's and Gaenslen's procedures, the Laquer sign, Yergason's chair test, and forcible compression of the sacro-iliac joints.

Laboratory Data. Roentgenograms in traumatic arthritis may be negative or may reveal a variety of alterations: capsular distention from synovial exudate in early cases; destructive and proliferative changes in cases wherein acute trauma is followed by chronic progressive arthritis.[9, 10]

The cell count of normal synovial fluid is as follows: total number of cells per cubic millimeter, $\pm$ 50; polymorphonuclears $\pm$ 5 per cent; mesothelial cells $\pm$ 3 per cent; monocytes $\pm$ 58 per cent; clasmatocytes $\pm$ 30

per cent. Forkner (1930) was not sure whether lymphocytes are present or not. In two cases of traumatic arthritis the cytology of synovial fluid was found by Keefer, Myers and Holmes [11] to be as follows: total cell count per cubic millimeter, 4,800 and 3,550; polymorphonuclears 94 per cent and 10 per cent; lymphocytes 3 per cent and 2 per cent; monocytes 0 and 42 per cent; clasmatocytes 3 per cent and 46 per cent.

[Counts on these two cases are noted because so few have been made in cases of traumatic arthritis.—Ed.]

Treatment. Conservative treatment consists of rest, supports or bandages, physiotherapy and graded exercises. A high percentage of Jepson's [9] patients who had traumatic backache recovered under his program which is outlined in detail. When conservative treatment fails, as occasionally it does, a fusion operation may be indicated.

Slight posttraumatic effusion in knee joints may be disregarded. When significant, the effusion may be reduced by application of compression bandages in conjunction with physiotherapy. When distention from fluid occurs recurrently, as a late sequel to injury of a knee, Glissan [12] reported that adhesions or weakened control by quadriceps muscles generally were found.

When arthritis follows contusion of articular cartilage, Key expressed himself in favor of excision of the degenerating cartilage. At first he hesitated to do this because his experimental resection of rabbits' cartilage generally had resulted in progressive arthritis. However, similar experiments by him on dogs and cats, and by Bauer and Bennett (1933) on rabbits, were not attended by arthritis unless postoperative patellar displacement occurred. Therefore, in his two cases, Key excised the injured cartilage and part of the affected synovia. The knees became asymptomatic.[8]

Gonorrheal Arthritis

In some cases articular complications of gonorrhea subside rapidly and completely in the course of treatment for the local infection, with or without special therapy for the joints. In many others the articular disease becomes progressive, producing marked destruction and limited motion. The varieties of articular involvement are: of the acute type, (1) arthralgia, (2) acute synovitis, (3) acute non-purulent arthritis (serofibrinous exudate) and (4) acute purulent arthritis; of the chronic type, (1) synovitis, (2) arthritis. Additional forms of "gonorrheal rheumatism" are tendinitis, myositis, and keratodermia blenorrhagica (with arthritis). The patient's resistance, the virulence of the particular bacterial strain infecting him and the type of treatment used, determine the type of articular disease and the prognosis of the latter. Several interesting studies on various phases of gonorrheal arthritis are current.

Clinical Data. Of 69 cases of gonorrheal arthritis studied by Keefer

and Myers [13] 58 of the patients were males and 11, females. Their ages varied from 18 to 70 years. The time between the onset of the primary gonorrheal infection and the arthritis could not always be determined because of the presence, in some cases, of old infections of the genito-urinary tract of indeterminate duration, reinfections, or the appearance of exacerbations in the genital tract. Joints became involved generally within 10 to 21 days after the initial infection; in three cases, within two to six months thereafter, and in one, simultaneously with the initial infection. In three cases evidence of local gonorrhea had disappeared. It is again pointed out that polyarticular invasion (present in 60 cases, or 87 per cent) is more common than monarticular involvement (present in nine cases, or 13 per cent). Any or many joints may be attacked, but knees, ankles, and wrists were most frequently involved; hands, shoulders, and feet, less often. Heels were affected in only seven cases; a sternoclavicular or a costosternal joint, in two cases.

[A chill is often an early symptom. An acute migratory polyarthritis or polyarthralgia which recedes in favor of an acute and more stubborn monarthritis is a feature of many cases, and one of considerable diagnostic significance.—Ed.]

Tenosynovitis often accompanied involvement of ankles or wrists. In 33 cases it was the feature which dominated the clinical picture. Tendon sheaths most frequently affected were those about the internal and external malleoli, and those over the dorsum of hands and feet; less frequently those about knees, palms, or heels were affected.

When periarticular redness, pain and thickness were marked, extensive effusions appeared and aspirations of joints yielded 40 to 165 c.c. of fluid. Periarticular muscular atrophy, sometimes marked, was present in all cases. Genital infections present were prostatitis in 54 cases, urethritis in 43, cervicitis in 10, epididymitis in five, and seminal vesiculitis in one. Abscess of Cowper's glands, of Bartholin's glands, and of Skene's glands each occurred once.

Temperatures of 99 to 103° F. were generally present. Salicylates gave insignificant relief, a point of value in distinguishing this disease from acute rheumatic fever. The leukocyte count varied between 9,000 and 23,000 per cubic millimeter of blood; the percentage of polymorphonuclears, between 70 and 88. Sedimentation of erythrocytes was rapid in all cases, varying from 0.4 to 1.7 mm. per minute (method of Erstene and O'Rourke).

Complications. In Keefer and Myers' [13] series, in 16 cases (23 per cent) catarrhal conjunctivitis developed, generally before, occasionally with, the arthritis. Three patients had iridocyclitis and conjunctivitis, one had endocarditis, and two had perichondritis of the cricoid cartilage, causing painful swallowing. The association with acute polyarthritis of some of these complications, especially the combination of tenosynovitis and perichondritis, may be helpful in suggesting the gonococcal nature of a case of arthritis.

Arterial thrombosis in association with gonorrhea is rare (Welch 1909). Mead and Stewart [14] reported the case of a patient with acute gonorrheal polyarthritis and salpingitis. After she was given 8 c.c. of milk intramuscularly, a general reaction culminated in peripheral arterial thrombosis necessitating amputation of three gangrenous toes. Mead and Stewart found no previous record of arterial thrombosis after injections of milk and concluded that the gonorrheal arthritic infection may have induced the thrombus.

[Five cases of acute thrombosis, involving the iliac, popliteal, or femoral arteries, after typhoid vaccine had been given intravenously are noted by Hench (1932) in his list of unusual reactions to such treatment. In two cases amputation was necessary. Several untoward reactions to milk were also listed; not thrombosis, however. It seems likely that the thrombosis in the case of Mead and Stewart may have been an unusual reaction to the foreign protein of milk and may have had nothing to do with gonorrhea.—Ed.]

Pathology. The classification of articular complications, as noted heretofore, indicates the variety of pathologic reactions which may occur. From the observations of Keefer, Parker and Myers [15] on the different pathologic reactions, it would appear that the prognosis in a given case of gonorrheal arthritis depends on how severely the surface cells of the synovia are involved. The pathologic reactions in knee joints were studied in two cases that came to necropsy. In one case the synovial membrane was essentially normal, but the subsynovial connective tissue was markedly congested, edematous, and infiltrated with a marked cellular reaction. Thus the patient presented a subsynovitis with involvement of subsynovial tissues, rather than a synovitis involving superficial synovial cell layers. Gonococci were not recovered from synovial fluid. In the second case the subsynovial connective tissues were not extensively involved, but the more superficial layer of synovia was markedly affected and largely destroyed. Numerous gonococci were found in synovial membrane and fluid.

From these comparative studies Keefer, Parker and Myers concluded that the less the superficial synovial cells are involved and the more the inflammatory reaction is confined to subsynovial or the more frankly extra-articular (periarticular) tissues, the better is the prognosis as far as preservation or restitution of function of a joint is concerned, and the less the chance of isolating gonococci from synovial fluid or tissues. When "infected exudates" are present the more serious types of gonorrheal articular disease are probably present.

Significance of Laboratory Data. Although certain features of the clinical picture, in conjunction with an honest history, are sufficient for a presumptive diagnosis of gonorrheal arthritis, conclusive evidence should always be sought by laboratory investigations. Conclusions on the value of such data, particularly smears from the genito-urinary tract, have been summarized in the first report of the Neisserian Medical Society of Massachusetts.[16]

The Society's report included a discussion on organisms resembling gonococci, criteria necessary for a diagnosis of presumptive, as well as of proved, gonorrhea in males, females and infants, the significance of extracellular, as compared to intracellular, gram-negative organisms, and the likelihood of obtaining "negative smears" in certain cases of gonorrhea. The report is recommended to those of limited experience in this field, particularly to those faced with a doubtful case of gonorrhea or gonorrheal arthritis.

Cultures of gonococci: It was the opinion of members of the society (February, 1934 [16]) that, to date, culture of gonococci, as a routine laboratory procedure, is impracticable, and that there is no practical method for sending material to a central laboratory for culture.

[A new culture method for the identification of *Neisseria gonorrheae* has been recently elaborated by McLeod and his colleagues.[17] Its value has been confirmed by Leahy and Carpenter [18] and the method has been simplified by Thompson.[19] Cultures are apparently simple to make and the results reliable; indeed some workers are finding them more reliable than the isolation and identification of gonococci in smears.—Ed.]

Cultures of synovial fluid from 40 patients who had gonorrheal arthritis, and who were seen by Myers, Keefer and Holmes,[20] were positive for gonococci in only 25 per cent of the cases. Judging from pathologic studies noted in the foregoing,[15] these workers believed that negative cultures or smears from synovial fluid in cases of gonorrheal arthritis result not from faulty technic but because infection is localized beneath and not on the synovial surface. As has been mentioned, when the inflammation is essentially subsynovial, and when the superficial cells of synovia are not much affected, the cell-membrane on the surface is intact, organisms do not get into the synovial fluid, and if an exudate is present it is a non-infected one. Gonococci can be isolated with ease in smears or cultures of synovial fluid only when the synovial surface membrane is the site of an intense inflammatory reaction; in such cases organisms have advanced from periarticular tissues into the cells of the synovial surface and thence into the synovial fluid; hence exudates are infected.

Complement fixation test: The complement fixation (Schwartz-McNeil) test for gonorrhea is in principle similar to the Wassermann test for syphilis. Members of the Neisserian Society expressed the belief that it is of limited value: it is usually negative in cases of acute gonorrhea, for sufficient changes have not had time to occur in the blood.

[It is rarely positive during the first 10 days of infection.—Ed.]

It frequently remains positive for months or years after the disease is "cured" by clinical or other laboratory standards, and false positives and false negatives may occur. A positive test, however, may serve as evidence confirmatory of other data.

According to Keefer, Myers and Holmes,[11, 20] however, the test is of distinct value. The test was positive on the blood serum in 80 per cent

(45 of 55 patients [18]) to 86 per cent (37 of 43 patients [21]) of their cases of gonorrheal arthritis "at some time during the course of the disease." In about 90 per cent of these cases the test was positive on the first examination. It was negative in some cases in which genital infection had been present for no longer than two weeks. The test was positive on synovial fluid in from 71 per cent (17 of 24 cases [21]) to 76 per cent.[11] In the majority of cases tests on blood and synovial fluid were in agreement. Occasionally the reaction was positive on blood serum, though not yet positive on synovial fluid. When differences were noted, the blood serum, except in one case, gave a positive reaction before synovial fluid gave such a reaction. Therefore, there is no advantage in testing synovial fluid rather than blood. In three cases very early in the disease, gonococci were found in synovial fluid, but complement fixation tests on blood and synovial fluid were negative. In three other cases it was possible to watch the tests change from negative to positive. In cases in which both syphilis and gonorrhea were present a positive Wassermann reaction did not disturb complement fixation of gonococcal antigens.

Tests were done on 71 controls: 24 patients who had rheumatic fever, 30 who had atrophic arthritis, and 17 who had other articular diseases (tuberculous, hypertrophic or hemolytic streptococcic arthritis or Charcot's joints). A positive test was obtained from only two: a 14 year old boy who had rheumatic fever, and a girl who had rheumatoid arthritis and psoriasis. A doubtful test was obtained in a case of rheumatic fever accompanied by old, proved gonorrheal prostatitis.

The investigators concluded that the routine use of the test on patients who have arthritis seems indicated and that a positive test is highly suggestive of the gonorrheal nature of an arthritis. Tests should be repeated in all cases, especially when their results seem at variance with other data. However, when the history and clinical findings suggest gonorrheal arthritis, but organisms cannot be isolated from synovial fluid or the genital tract, a positive test on blood or synovial fluid affords data of diagnostic worth.

[These interesting studies need confirmation. Such a test, if reliable, would be of much value. The authors omitted certain desirable details. They stated that a certain number of tests were positive "at some time in the course of the disease." More data should be given regarding the initial positivity of the test in relation to exposure to infection, and to the appearance of genital and articular disease. Controls should include normal persons as well as patients who have various articular diseases.—Ed.]

Other tests on synovial fluid: Cell count: The total cell count on infected fluids varied between 7,350 and 158,000 per cubic millimeter, and on non-infected fluids from 1,800 to 78,250.[20] Polymorphonuclear leukocytes formed 46 to 100 per cent of the cells. Clasmatocytes and monocytes were commonly present, in a ratio of 1 to 16 per cent and 1 to 33 per cent respectively. Lymphocytes varied from 1 to 33 per cent; rarely was the percent-

age more than 10. In infected fluids the percentage of polymorphonuclear cells was always more than 76. Non-infected fluids generally contained more monocytes and clasmatocytes than infected fluids.[20]

Chemical determinations: The concentrations of total protein, non-protein nitrogen, and sugar in blood and synovial fluid were determined,[20] but the data were not of diagnostic value. Estimations of total protein were of significance only as they, with the cell counts, indicated the presence of an exudate, not of a transudate. According to Forkner (1930), since bacteria utilize sugar in their metabolism, a low concentration of sugar in synovial fluid in a case of arthritis suggests bacterial arthritis, and the lower the concentration of sugar the greater the likelihood of positive cultures being obtained from joint-fluid. Myers and his colleagues [20] found that the concentration of sugar in synovial fluid depended on three factors—the concentration of sugar in the blood, the synovial leukocyte count, and the presence of microörganisms in the fluid—but that of the three factors the first two were more important than the third. Inasmuch as a low concentration of sugar was found in non-infected synovial fluids, a reduced concentration of sugar did not always indicate the presence of organisms. Thus, Forkner's generalization was upheld, but only in part.

Treatment. Fever therapy: Accumulating evidence indicates that fever therapy is the treatment par excellence for gonorrheal arthritis and that in the majority of cases not only are articular lesions markedly and promptly benefited thereby but also gonorrheal lesions elsewhere in the body. In 12 cases of acute gonorrheal arthritis treated by Simpson [22] with radiothermy or with heated, air-conditioned cabinets, results were uniformly successful and all patients became free of symptoms. Jones [23] expressed the opinion that fever therapy is practically specific in such cases. All of his 10 patients who had acute gonorrheal arthritis, of three to 12 weeks' duration, were "cured." Joints became symptom-free and urethral discharges generally ceased after two to five treatments. Hedrick [24] also noted marked improvement in one acute case. "Striking results" were obtained by Kovacs [25, 26] even in cases of stubborn chronic gonorrheal arthritis. Doses of fever generally preferred are five hours at 105 to 106.5° F. Two to six sessions of fever are generally given, one about every four days.[22, 27]

Fever therapy is a highly specialized form of treatment. The Council on Physical Therapy of the American Medical Association [28] has recommended that the technic of its administration be given as much study as a surgeon gives his specialty. It should be administered only by a trained personnel under the supervision of a physician familiar with the reactions. Under such circumstances fever therapy is an essentially safe procedure. However, The Council's report lists 29 deaths among 4809 patients who had various diseases which were treated by hyperpyrexia (a mortality of 0.6 per cent).

[Many of the deaths undoubtedly were of patients who had neurosyphilis, and some deaths should be ascribed to the disease, not to the treatment.—Ed.]

Other measures: Where fever therapy is not available, older methods must be invoked. The usual forms of therapy for gonorrheal arthritis were listed by Hedrick,[24] and include administration of stock and autogenous vaccines, intramuscular injection of autogenous synovial fluid, foreign protein therapy, administration of convalescent serum, injection of the prostate gland and seminal vesicles with various chemical substances, intravenous injection of mercurochrome, deep roentgen therapy, aspiration, and irrigation or open drainage of joints. In addition to certain of these measures, Hedrick expressed himself in favor of intravenous injections of ammonium iodoxy benzoate, twice a week, four to 10 injections in all; aspiration or irrigation of joints and insufflation with air, and in refractory cases, fever therapy.

[The wave of enthusiasm for ammonium iodoxy benzoate and allied substances in cases of atrophic arthritis has about run out.—Ed.]

Aspiration of large effusions generally gives considerable relief of pain.[13] Particularly in cases of gonorrheal pyo-arthrosis are aspiration and irrigation indicated.[24] Irrigation with 1 to 5000 solution of mercuric chloride is a method for which Oxford [29] expressed favor. Insufflation of air, as proposed by Porter and Rucker (1929) has the approval of some. After aspiration, 75 to 100 c.c. of air [30] are injected, or enough to create a pressure of 40 mm. of mercury.[24] The air is absorbed in three to four days and insufflation can be repeated. Presumably the air helps to prevent adhesions by keeping synovial folds apart. It is suggested, also, that nitrogen mixed with the injected air may inhibit growth of gonococci. Taylor [31] approved injection through the rectal mucosa, into the prostate gland, of Pregl's iodine solution. Excellent results not only for the genital infections but also for the arthritis have been claimed by him and by others.

Prognosis and Results of Treatment. In a given case, prognosis is difficult. Some patients recover rapidly without permanent disability. In many cases the disease results in progressive, chronic arthritis with restriction of motion or ankylosis. Reinfection occasionally retards healing. The poorest results seen by Myers, Keefer and Holmes [20] were in cases in which the cell count of the synovial fluid was more than 40,000 per cubic millimeter and the fluids were infected. In such cases residual chronic arthritis often eventuated. Those patients who recovered completely were as a rule those who had non-infected fluids, in which the leukocyte count was low, or infected fluids in which the leukocyte count was low. Even so, the outlook for complete articular recovery was not good. Only 37 per cent of the 69 patients recovered without signs of disease of joints.

[These statements presumably refer to cases in which treatment was other than by fever therapy. As we have noted, results therewith are very much better than with other forms of treatment, especially when the arthritis can be treated by fever therapy within the first two to four weeks of its onset.—Ed.]

Tuberculous Arthritis

The incidence of tuberculous arthritis is on the decline, partly because of certification of herds and pasteurization of milk. Tuberculous arthritis is always secondary to a tuberculous lesion elsewhere in the body. The infection is blood-borne to joints. Henderson [32, 33] found that various joints were affected by tuberculous arthritis in the following order of frequency: spine, knee, hip, elbow, ankle, shoulder, wrist. Symptoms are stiffness, pain, local increase in temperature, swelling, deformity and, if the lower extremities are involved, limp. Children give "night cries," adults experience "night jerks"; the latter are attributable to muscular relaxation, followed by sudden contraction in sleep. Tuberculous arthritis is persistently chronic although incomplete remissions occur. When it afflicts adults it is generally monarticular, although it may be polyarticular; it is more often polyarticular when it affects children than when it affects adults.

Of 274 proved cases of tuberculous arthritis of a knee seen by Henderson, in two-thirds the patients were males. Trauma was an inciting or precipitating factor in 13 per cent. Only 8 per cent of patients gave family histories of tuberculosis. In 44 per cent of cases tuberculosis was found elsewhere in the body. In 91 per cent articular bone was involved; in 9 per cent only synovia was affected. In 50 per cent bone abscesses were present; in 11 per cent, sequestra occurred.

Roentgenograms. Henderson expressed agreement with his colleagues, Ghormley, Kirklin, and Brav,[34] that roentgenograms, although often characteristic, do not give incontrovertible evidence. Comparing the alterations in 65 cases in which the presence of tuberculous knee joints was proved, to those in 11 cases of non-tuberculous arthritis (gross and microscopic sections also being studied) Ghormley, Kirklin and Brav found them to be essentially similar. In very early tuberculosis, roentgenographic signs were absent. For a time, in the non-tuberculous case more change will be seen than in the tuberculous case. Marginal erosions, and long preservation of articular spaces were seen in both but were more suggestive of tuberculous involvement. Marginal lipping, seen in both, was more often present in non-tuberculous cases. In tuberculous arthritis, areas of greatest destruction of cartilage or bone were either central or marginal; in non-tuberculous arthritis destruction was practically always central. Bone abscesses and sequestra indicate tuberculous arthritis, but in a large percentage of cases sequestra, when present, were not visible in roentgenograms. In one case of proved tuberculous arthritis of a knee associated with tuberculous spondylitis, seen by Bennet and Hinricson,[35] the roentgenographic appearance resembled that of a Charcot joint, and the latter diagnosis was entertained for a time particularly as the knee was painless.

Pathology. Herniation of joint cartilage into subchondral tissue and plication (folds or pleats) were frequently noted by Freund [36] in tuberculous joints, in which undermining of joint cartilage is extensive. It does not

lead to marked deformity of the surface of the joint because the entire cartilage usually becomes resorbed or sequestrated.

Synovial Fluid. The total cell counts of synovial fluid in five cases were found, by Keefer, Myers and Holmes,[11] to vary between 6,500 and 110,000 per cubic millimeter. The differential count was as follows: polymorphonuclears 45 to 93 per cent; lymphocytes 3 to 30 per cent; monocytes 1 to 31 per cent; clasmatocytes 1 to 7 per cent; eosinophiles 0 to 3 per cent. The differential formula thus disclosed no absolutely characteristic features, but there were generally more lymphocytes and monocytes than in other types of arthritis. Chemical examinations revealed no characteristic alteration: total protein per 100 c.c. of synovial fluid varied between 4.3 and 5.5 grams, the non-protein nitrogen of fluid equalled that of blood; the sugar of the fluid (91 to 160 mg.) was always a few milligrams higher than that of the blood (79 to 116 mg.).

[The sugar determinations on synovial fluid did not always represent fasting values.—Ed.]

Treatment. Henderson expressed the opinion that non-operative therapy is erroneously called conservative treatment. In fact surgical treatment, arthrodesis (at least if patients are more than nine years of age), may be more conservative, and more saving of time and money; even though it is granted that a few patients can be cured by long rest and articular fixation under supervision in hospitals. The knees, hips, shoulders, and spine are best suited for arthrodesis; the elbows, wrists, and ankles are next in choice. Of 274 cases of tuberculous arthritis of the knees, in which Henderson [32, 33] performed arthrodesis between 1913 and 1934, fusion resulted in about 90 per cent. Nine per cent of the patients were found to have died of their non-articular tuberculosis. Synovectomy was performed on four patients whose articular tuberculosis was confined to synovia. Of these four patients two were well and comfortable several years later.

"Tuberculous Rheumatism"

An extensive résumé of literature on this subject has been made by Brav and Hench.[37] As described by its proponents, this condition is a form of polyarthritis, simulating in some cases acute rheumatic fever; in other cases, chronic atrophic arthritis, but bearing some etiologic relationship to tuberculosis. It is thought to be attributable to a tuberculous toxin from some distant focus, a filtrable virus, an attenuated form of the bacilli of tuberculosis, or an allergic reaction. True tubercles are not the expected finding, and when present, they indicate superimposed tuberculous arthritis rather than tuberculous rheumatism. Evidence for the diagnosis of tuberculous rheumatism includes familial tuberculosis, associated visceral tuberculosis, demonstration of Koch's bacilli in synovial fluid and the blood stream, positive results of inoculation of guinea pigs with joint-fluid, and in some cases the presence of a typical tuberculous joint before, coincident

with, or subsequent to, the development of polyarthritis. Reported pathologic findings have included focal collections of round cells, of plasma cells and of histiocytes; isolated instances of necrosis, internal thickening and vacuolization of the vessels, and the presence of giant cells and endothelial cells. These alterations are considered either a transition stage between simple inflammatory tissue and tuberculosis, or an allergic manifestation of the latter.

Against acceptance of the syndrome of tuberculous rheumatism have been arrayed a large number of competent investigators who argue that there is no adequate clinical method of identifying it, no consistently characteristic roentgenographic evidence, no experimental or laboratory evidence in its favor that is not highly controversial, and no consistent demonstration of its supposedly characteristic microscopic pathology.

A statistical study by Brav and Hench of a series of 150 cases of acute rheumatic fever and 250 cases of chronic atrophic polyarthritis revealed no significantly higher incidence of familial tuberculosis or associated visceral tuberculosis than that found among 250 control cases. The controls were consecutive non-arthritic cases, studied in the same period as the arthritic series. The control patients registered a multiplicity of complaints in no way related to joints. Of a series of 75 cases in which a diagnosis of chronic atrophic polyarthritis had been made, and in which the pathologic characteristics of a single joint were determined by microscopic examination of tissues or by inoculation of guinea pigs, the joints of eight patients were found to be definitely tuberculous. In each of the eight cases, the tuberculous nature of the arthritis was suspected prior to examination of tissue or inoculation of animals, but the presence of polyarthritis was confusing. Brav and Hench concluded that further investigation will be required to determine the acceptance or rejection of the syndrome of tuberculous rheumatism. At present, they concluded that no incontrovertible proof of such an entity exists.

LeSage,[38] however, accepting the entity without question, was surprised how seldom the condition was diagnosed and how often it was confused with gonorrheal or gouty arthritis. He admitted that generally no direct proof of its tuberculous nature can be found either on pathologic or bacteriologic examinations. "We have only clinical signs to guide us," he wrote. In a few cases, although cultures and examination of the joints may be negative, the subcutaneous or intraperitoneal inoculation of bacteriologically-negative synovial fluid into guinea pigs will produce tuberculosis. LeSage expressed the belief that a tuberculous virus may manifest its presence in serous membranes only by ordinary, simple, inflammatory lesions in the "pre-bacillary stage." In the later "bacillary stage" the primary inflammatory lesions undergo evolution to the state wherein their tuberculous nature may be revealed.

In evidence, LeSage included the following cases. A man, aged 26 years, in 1923 had vague pains and stiffness in the neck and spine; inflammation and ankylosis of the right ankle. The case progressed as follows: in 1924, involvement of the left ankle; in 1925, of the temporomandibular joint, with orbital neuritis; in 1926, progressing "rhizmorphous spondylitis"; in 1930, swelling of the left knee; in 1931, left orbital neuritis, corneal ulcerations and amaurosis; in 1932, involvement of the right knee, and in 1933, involvement of both shoulders. Roentgenograms disclosed the following: those of the thorax "ganglionic spots with dense peribronchial and pulmonary fibrosis"; those of the joints, destructive arthritis, exostosis and rarefaction. Fluid removed from the right knee in 1932, when injected into guinea pigs, produced extensive tuberculosis, and bacilli were recovered.

A woman, aged 61 years, had arthralgia of the feet and effusion of the left knee. She presented no evidence of tuberculosis. The cutaneous reaction was positive for tuberculosis. Fluid from the knee joint was negative, as was the guinea pig test, but culture of the patient's blood (Löwenstein's technic) gave colonies of virulent Koch's bacilli after three weeks.

From such evidence, LeSage concluded that lesions of inflammatory tuberculosis (ante-bacillary period) are attributable to a filtrable virus, whereas specific lesions are produced by Koch's bacillus.

[In three other cases the diagnosis seems to have been made chiefly from clinical data, data which may have been clinically unmistakable to LeSage, but perhaps inadequate for others.—Ed.]

To Buckley [39] much of the evidence for the entity was unconvincing. Positive cutaneous reactions may easily be attributable to latent tuberculous foci in lymph nodes or elsewhere, and isolation of bacilli of tuberculosis from the blood in cases of acute polyarthritis, by the method of Reitter and Löwenstein (1932), generally has been unsuccessful in other hands. In two cases of chronic polyarthritis, Buckley found bacilli of tuberculosis in effusions from knee-joints. Admitting the possibility that a chronic tuberculous focus in lymph nodes, or elsewhere, may sensitize tissues to, and thus favor infection by, streptococci, it seemed more probable to Buckley that sensitization is first produced by streptococci and that infection by bacilli of tuberculosis occasionally follows.

Pneumococcal Arthritis

This rare disease occurs only once in every 800 to 1000 cases of pneumonia. When pneumococci gain access to a joint they produce acute, generally purulent, arthritis. Fagge [40] reviewed the literature, and the experience of the physicians of Guy's Hospital between 1918 and 1932, during which years only seven cases, including at least two that were doubtful, were seen. Three-fourths of cases of pneumococcal arthritis occur in conjunction with pulmonary infection, generally after the stage of resolution, occasionally in the stage of red hepatization. A fourth of the cases occurs in association with pneumococcic septicemia but without pneumonia. Larger joints are generally involved, the knees most commonly; next in frequency of involvement are the shoulders, wrists and elbows. In three-fourths of

cases the involvement is monarticular. When pneumonia is present the appearance of acute arthritis raises the suspicion of its pneumococcic origin. Otherwise the diagnosis is made on bacteriologic examination of aspirated joint-fluid. In spite of purulent exudates and gross involvement, complete articular restitution often occurs and ankylosis is rare. Of patients so affected, 24 per cent die from non-articular pneumococcic infection.

Of Fagge's patients, one had pneumococcic meningitis, and a shoulder was affected; one had pneumonia and a knee was involved; one acquired influenza shortly after spraining an ankle, and pneumococcic abscesses developed about the affected ankle. In the cases at Guy's Hospital, pneumococcus type I was found once, type III, twice.

Farah [41] described a different course of presumed pneumococcic arthritis in one case:

A man, aged 31 years, acquired a sore throat and bronchitis in 1924. Fifty days later subacute, febrile monarthritis of the right knee developed and was evident for a few days. Complete restitution occurred. In July 1924, without any associated sore throat, the left knee became similarly involved and remained involved for 20 days, but recovery was complete. In December 1925, three days after onset of a sore throat, the right knee and left wrist were briefly affected; in February 1927 the patient again had a sore throat and an involved right knee. In the next six years he had repeated mild attacks in one to three joints, occasionally after onset of a sore throat or cold. These and all previous attacks apparently responded notably to salicylates. In February 1933, generalized febrile polyarthritis developed. Roentgenograms of joints were normal in spite of repeated involvement through 10 years. The heart was normal. From the blood pneumococci were obtained in pure culture. From the red throat, pneumococci, type III were obtained and agglutinins thereof were present in the serum in a titer of 1 to 2000. Skin tests to several bacteria were negative, but to the pneumococci obtained from the patient were strongly positive. Articular cultures were not permitted.

Farah assumed the case to be one of an unusual form of pneumococcic arthritis from focal infection (pneumococcic sore throat), of special interest because of the absence of purulent effusion or articular residues, and because of the later resemblance to acute rheumatic fever, including response to salicylates. He suggested that other cases of acute rheumatism may be so caused.

[It is to be noted that the early attacks were monarticular, not typical of rheumatic fever. Somewhat similar cases of recurrent monarthritis and polyarthritis of short duration, leaving no residue in joints or heart, have been reported as instances of allergic arthritis. This report should stimulate appropriate investigations in unclassifiable cases. One of us saw a case in which a parotitis was the only infected focus. Pneumococci could always be isolated from saliva but not from joints.—Ed.]

Pathology. Details of pathologic reactions in a case of pneumococcic arthritis of an elbow joint were described by Keefer, Parker and Myers.[15] An intense inflammatory reaction of synovia—thickening of subsynovial fibrous tissue and destruction of synovial surface cells—and extensive destruction of cartilage and subchondral bone were noted.

Treatment. Immobilization, prompt articular aspiration and irrigation with physiologic saline solution, repeated as necessary, are advocated.[15, 39]

Scarlatinal Arthritis; Postscarlatinal Rheumatism

In the course of, or following, scarlet fever the joints or heart may be affected in about 6 to 10 per cent of cases by (1) toxic lesions appearing early in the disease, (2) septicopyemic lesions appearing early or late, and (3) so-called allergic lesions which generally appear late. Both the suppurative and the non-suppurative varieties of scarlatinal arthritis, or postscarlatinal rheumatism, have been considered by some to be more or less specific manifestations or complications of scarlet fever. Others believe that the non-suppurative forms, with or without carditis and with or without a previous history of rheumatic fever, should be regarded as forms of true rheumatic fever, activated by the hemolytic streptococcal infections of scarlet fever in the same way that other streptococcal infections are prone to activate latent rheumatic fever. Comparing epidemiologic studies in cases of postscarlatinal rheumatism with those in cases of rheumatic fever, Paul, Salinger and Zuger [42] expressed agreement with the latter viewpoint. A high incidence of rheumatic fever was found in families of patients who had had postscarlatinal non-suppurative arthritis or carditis. The clinical course of these two complications is essentially similar to that of rheumatic fever. Although every case of non-suppurative arthritis or carditis following scarlet fever is not necessarily a manifestation of rheumatic fever, the majority probably are, and are not specific complications of scarlet fever.

The case of a boy 14 years of age, who suffered from fever and a red, swollen hip a few days after inoculation against scarlet-fever was reported by Stewart.[43] In the next five months, while the patient remained in bed, destructive arthritis and marked stiffness of the hip appeared. Since, in roentgenograms, the epiphyseal line seemed open and motion of 10° was present, motion was encouraged. Finally flexion of 40°, hyperextension of 10°, and rotation of 30° were accomplished by the patient. At last he could sit in a chair and walk a mile and a half without pain. Fluoroscopy gave evidence of pseudo-arthrosis, motion originating wholly in the epiphyseal line.

[Bacteriologic studies relative to the hip apparently were not made, and the data furnished do not permit a positive diagnosis.—Ed.]

Syphilis Affecting Joints

Clutton's Joints; Symmetrical Serous Synovitis. The most common articular affection of congenital syphilis among children is Clutton's joint, a relatively painless, simple, serous or gummatous synovitis which is generally bilateral, lasts for months or years, and is not accompanied by bony changes. It generally affects one or both knees, one being affected some

time before the other. Elbows, wrists or fingers are less frequently affected. It is uncommon among adults who have acquired syphilis. When present it usually precedes or accompanies the secondary eruption. Of 363 cases of congenital syphilis encountered by Klauder and Robertson,[44] in 63 Clutton's joints were present; one or both knees were involved in all, and in two an elbow also was affected. Little or no pain, tenderness, heat, redness, limitation of motion, or muscular atrophy were present. The patients were generally from eight to 15 years of age. Pathologic reactions include formation of villous processes and synovial fringes and simple or gummatous synovitis. Untreated, the process becomes chronic but generally terminates spontaneously. Antisyphilitic therapy may affect it markedly or not at all. Splints, rest and surgical operation seem useless. In all of Klauder and Robertson's cases effusions eventually disappeared without ankylosis. If ankylosis is present the condition is not Clutton's joint but may be syphilitic arthritis. Patients who have Clutton's joints are more likely than others to suffer from interstitial keratitis.

Eleven cases of chronic synovitis of the knees, with persistent or recurrent effusions, were seen among children by Gill and Orr [45] and were considered very similar to cases of Clutton's joint although Wassermann reactions on blood and spinal fluid were negative in all but two. In one of the latter a positive reaction was obtained only after administration of provocative doses of neoarsphenamine. Tissue obtained in one case revealed a red, thick synovial membrane, synovial fringes and early formation of pannus, with some erosion of underlying cartilage.

[Gummatous infiltrations were not mentioned.—Ed.]

Although the etiology was undetermined, all the cases were thought possibly to be syphilitic. In similar cases Klauder and Robertson recommended provocative tests. Only one case was cured by therapy: Buck's extension, casts, splints, braces, physiotherapy, heliotherapy, compression bandages, repeated aspirations.

[Antisyphilitic therapy apparently was not administered. It seems to us that one has no right to make or suggest a diagnosis of Clutton's joint in a patient with negative Wassermann reactions on blood and spinal fluid unless the parents reveal evidences of syphilis, or the patient shows stigmata of congenital syphilis. Some believe that conservative treatment of Clutton's joints is generally followed by recovery whether or not specific antisyphilitic treatment is administered.—Ed.]

Syphilitic Arthritis. The Wassermann reaction was performed by Keefer, Myers and Holmes [11] on four specimens of synovial fluid from two patients who had syphilitic arthritis. The blood serum and synovial fluid were positive on three occasions; once the reaction of blood serum was positive when that of synovial fluid was doubtful. In two cases the cytology of the synovial fluid was as follows: total cells per cubic millimeter 3,200 to 4,500; polymorphonuclears 17 to 52 per cent; lymphocytes 35 to 51 per cent; monocytes 7 to 32 per cent; clasmatocytes 3 to 16 per cent. In one

case the total concentration of protein in the synovial fluid was 3.8 gm. per 100 c.c.; of sugar, 78 mg.; of non-protein nitrogen, 24 mg.

Undulant Fever

The symptomatology of this disease was reviewed by Miller.[46] An almost constant symptom is arthralgia, sometimes severe enough to suggest acute arthritis. In some cases articular pain and tenderness are present, but no swelling. Some cases resemble instances of acute rheumatic fever. If the patient has an afebrile period, the joint disturbance may largely subside. In one of Miller's seven cases, the spindle-shaped swellings of the fingers resembled those seen in atrophic arthritis; and in this case the diagnosis of atrophic arthritis had been made. An intermission in the fever was followed by disappearance of the swellings. Suppurative arthritis of costosternal or costochondral junctions, and suppurative spondylitis, have been reported by others. Blood cultures, when positive, as they are in only 25 per cent of cases, establish the diagnosis. Agglutination tests are useful but variably positive; in many active cases they are negative unless repeated frequently.

A case of undulant fever, resembling a case of acute rheumatic fever, was seen by Twedell and Schlotzhauer.[47] A young man had sore throat, malaise, pains in the chest and right knee, and later had headache, cough and fever. In a few days the pain in the knee disappeared but migratory pains affected the opposite leg, shoulders, and elbows. A diagnosis of rheumatic fever was made but the effect of salicylates was poor. A month later an enlarged spleen was noted. Several blood cultures revealed *Brucella abortus* and agglutinins were present in a titer of 1 to 1,600.

Treatment. According to Miller, treatment with specific vaccines and chemotherapy is not of proved value. Occasional results from typhoid vaccine or arsphenamine are reported. In a case of three months' duration, seen by Jones,[28] one session of fever therapy (two and a half hours at 105.5° F.) was followed in a few days by complete cessation of malaise, weakness and fever.

[Arthritis was not mentioned as being present in this case.—Ed.]

Experimental Undulant Fever. Feldman and Olson [48] were unable to produce demonstrable lesions in swine by injection, by various routes, of strains of *Brucella abortus* of porcine origin, consistently pathogenic to guinea pigs. Agglutinins were produced in the blood serum of all animals that received injections. Although the strains had been isolated from lesions of spontaneous spondylitis of hogs, no similar lesions could be reproduced experimentally. It is concluded that the apparent predilection of such organisms for vertebral bodies does not represent an inherent tendency of the organism for elective localization, but that the predilection is accidental or casual.

Haverhill Fever; Erythema Arthriticum Epidemicum

Full details of this disease, one of recent identification (Levaditi, Nicolau, Poincloux; Place, Sutton, Willner; 1926) were given in three reports. Haverhill fever has four main characteristics: (1) an abrupt onset with chills, fever, malaise, vomiting and headache; (2) an early eruption, rubelliform or morbilliform, occasionally first, and often only, on the extremities, especially about the ankles and wrists, with a tendency to become hemorrhagic; (3) multiple arthritis of varying, but often of severe, degree. and (4) a peculiar remittent (saddleback) fever curve, of abrupt rise, with remission in from two to five days, and after a few days of relative freedom from symptoms a febrile recurrence with which the arthritic manifestations appear.[49]

Symptoms referable to joints are outstanding and distressing. Generally they appear with the secondary rise of fever, on the third to the fifth day of the disease, very occasionally later. Several joints may be attacked, the wrists, elbows, knees, shoulders, fingers and ankles most commonly. Joints may be markedly painful; redness and swelling are variably present. Roentgenograms of joints are negative. Muscles are "lame" but not tender. Hydrops is often present in a knee, and in two cases pure cultures of the causal organism, *Haverhillia multiformis,* have been isolated therefrom.[49, 50] The arthritic symptoms may last from a few days to several months, but generally they last about four weeks. They may persist longer than the fever. In general, articular restitution is complete or almost so.

The condition must be distinguished from rheumatic fever, which has no such peculiar fever curve, from dengue, from infectious erythema with arthralgia, from erythema multiforme, from Malta fever, and from rat-bite fever. In Haverhill fever the heart is negative, and although sore throat is a common symptom it is a diffuse catarrhal type of injection without exudate or tendency to involve lymphoid tissue, such as is seen in rheumatic fever. The diagnosis is confirmed by isolation of the specific organisms from the blood or from joint fluid. Specific agglutinins are present. Unpasteurized milk is believed to be the usual source of infection, but Scharles and Seastone[51] have shown that the condition may follow a rat bite. A medical student who was bitten by a laboratory rat acquired the disease, and it was identified by agglutination tests and by recovery, by Bauer, in fluid from an ankle, of the specific organism of Haverhill fever. All attempts to find spirilla of rat-bite fever failed. It is suggested that certain cases of supposed rat-bite fever may in fact be cases of Haverhill fever.

Septic (Purulent) Arthritis

The common forms of septic arthritis, aside from the gonococcal form, are attributable to *Staphylococcus aureus* or to *Streptococcus hemolyticus.* A hip, a knee, or a shoulder is most commonly affected, and roentgenograms often disclose no abnormality for the first 10 days.[52] Early diagnostic

aspiration is recommended. Particularly if leukocytes number more than 15,000 per cubic millimeter of blood, and if thick pus is present, Oxford has expressed himself as in favor of arthrotomy with open drainage. Such treatment was necessary in 15 (60 per cent) of his 26 cases; in the remainder conservative therapy was permitted such as drainage by aspiration and then traction or fixation. Ankylosis, however, frequently results, particularly if the arthritis arose from infection (osteomyelitis) of juxta-articular bone. The most marked alterations in synovial cytology, noted by Keefer, Myers and Holmes,[11] were seen in three cases of arthritis caused by hemolytic streptococci. The total number of cells per cubic millimeter varied from 109,500 to 350,000, and polymorphonuclear cells constituted 94 to 100 per cent thereof.

The articular pathology in two cases was described by Keefer, Parker and Myers [15] and included synovial thickening and cellular infiltration, with regions of complete destruction, cartilaginous thinning and erosion; infiltration of leukocytes; abscesses in bone marrow, and masses of visible bacteria.

In four cases in which treatment was administered by Taylor,[53] transfusions were employed and bacteriophage seemed of value.

Arthritis of Subacute Bacterial Endocarditis

Pains of the joints commonly occur with infective endocarditis. The joints do not suppurate. Their pathology has not been described heretofore. In a case of subacute bacterial endocarditis affecting a young man, and attributable to an unidentified form of gram-negative coccus, Keefer, Parker and Myers [15] found the essential articular lesion in the synovial connective tissue with perivascular lymphocytic infiltration. The synovial surface cells were generally intact.

Meningococcic Arthritis

Brief clinical details of two cases, with pathologic reactions found at necropsy, were reported by Keefer, Parker and Myers.[15] Arthritis occurs in from 4 to 7 per cent of cases of meningococcic meningitis (Herrick and Parkhurst, 1919) and may assume three forms: *1.* One form comprises brief, early polyarthritis characterized by pain and tenderness but without swelling or hydrops, and generally accompanied by a hemorrhagic rash. The joint pains may be attributable to hemorrhages in articular and periarticular tissues. *2.* Metastatic pyoarthrosis with meningococci in the effusions is characteristic of the second form. Recovery occurs in one to four weeks, with or without ankylosis. *3.* Arthralgia from meningococcus serum constitutes the third form. From their studies, the writers [15] concluded that in meningococcic arthritis the metastatic lesion involves deeper synovial tissues first; later, the superficial cells, with effusion of fluid into the joint cavity and varying degrees of destruction of cartilage.

In a case in which chills, fever, jaundice, meningitis and meningococcic arthritis developed, and which was seen by Jaffé,[54] the use of meningococcus serum was followed by relief of all symptoms and signs, but the patient later died of pneumonia.

Rheumatic Fever

Incidence. Some studies indicate that the incidence of rheumatic fever depends largely on various factors of climate and environment: the patient's geographic habitat; his social condition; exposure to damp, cold and respiratory infections, and to seasonal change. Glover and others [55] have reminded us that the Medical Research Council's investigation, which included familial incidence and heredity, familial evidence of sore throats, maternal care, exposure, sleeping conditions, clothing, birthplace, occupation, income of parents, types and sites of houses, and so forth, concluded with the statement that the findings were largely negative. It is nevertheless felt by many that some of these factors are important, and Glover and Miller and others [55, 56] have voiced the general belief that the incidence of rheumatic fever and rheumatic heart disease is low in the tropics, higher in the temperate zone and among persons living near sea level or in basements, and also that it is higher in cold, damp months.

Geography. Reviewing the distribution of rheumatic heart disease, which is the best proof of the existence of rheumatic fever, in various parts of the world, Nichol [57] reported that it is prevalent and severe between latitudes 50° and 40° North, diminishes in warmer climates, is almost unknown between the Tropics of Cancer and Capricorn, increases again as cooler climates are reached and is common between latitudes 30° and 40° South. Thus it is practically unknown in the subarctics, in southern India, Puerto Rico, southern China, the Malay States and Panama. It is common among school children in England (1.5 to 2.0 per cent), northern Europe, northern United States of America (0.89 to 0.66 per cent), South Africa and Australia. Its incidence varies widely in the United States, from 0.86 in Boston to 0.45 per cent in Miami. Admissions to hospitals are more impressive, for a variation of 0.2 to 5.8 per cent exists, the latter in cold wet climates, and the former in warmer regions. Rheumatic fever and chorea are rare in Florida, according to Nichol (16 cases in 16,200 medical admissions to hospitals). Rheumatic heart disease is particularly rare among children born in Miami and is seen three times as often among children now living in Miami but born in the North. Of 103 patients who had rheumatic heart disease, seen in a given period, in only seven cases did it originate in southern Florida. Simmons [58] found the incidence of rheumatic heart disease in Kentucky to be the same as that in Texas and Louisiana, half that of Virginia and Maryland, and a fourth that of New England. According to Chase [59] it is rare in Oklahoma, a warm, dry state; it is becoming less frequent in Omaha, Nebraska,[60] and although it is increasing in the United States as a whole it is not increasing in New York City.[61]

Compared to its incidence in Great Britain, rheumatic heart disease is relatively infrequent in Australia. Cleland [62] found 116 cases (3.9 per cent) in 3000 postmortem examinations.

[Figures are not given to support some of these later statements.—Ed.]

Social Conditions. It is believed that the disease is more common in crowded cities than in the country, and that poor hygiene and environment favor its development. In Australia it is more common in the city and suburbs (194 of 218 cases came from the city and suburbs) than in the country, but it is common in the hill districts and low-lying valleys.[63] Although poverty is a factor, children of the poorest parents are less affected than those of less poor parents (Miller). Glover expressed the opinion that the true incidence of the disease is directly proportional to the degree of poverty, and that it is seen 20 to 30 times more frequently among children of the poor than among those of the well-to-do. The incidence of rheumatic heart disease was 48 per 1000 children in a public school in the poorest city district; 31 per 1000 children in public school in a better residential area. Thus, the former was one and five-tenths times higher than the latter; but it was moreover found to be eight times higher than the incidence among children of a wealthier class from urban private schools. From these figures, Paul, Harrison, and DeForest [64] concluded, again, that rheumatic heart disease is in part a manifestation of poverty.

Effect of Seasons. In England, rheumatic fever is more prevalent in the cold, damp months of fall and winter,[55] but in Rochester, New York, it is more common in late winter and spring.[65]

Heredity. A high family incidence is frequently reported; Swift [66] recently indicated that he still believed this phenomenon means an inherited state. Thus a hereditary tendency is present in a third of the cases, according to Benjamin,[67] who found that of 280 rheumatic children, 38 per cent had rheumatic parents and 17 per cent had rheumatic brothers or sisters.

Physical Type. Although the rheumatic child may differ from the normal one in other constitutional traits, he does not differ in physical type, as indicated by bodily dimensions, sexual differences, color of hair and eyes, type of contour (slender or thick) or posture, according to the exhaustive report of Young [68] who studied 1,212 children, 459 of whom were rheumatic, 368 asthmatic, and 385 normal.

Sex and Age. Juvenile rheumatism is more frequent among females.[65, 67] Of Kaiser's 1200 rheumatic children, 54 per cent were girls, 46 per cent, boys. Kaiser noted the disease infrequently among patients who were less than the age of three years; he found an increasing frequency among patients from three to 10 years of age, and a declining frequency among those from 10 to 15 years of age; thereafter the condition was as infrequent as it was before the age of three years. Only six cases of rheumatic heart disease of children less than two years of age have been reported. White (1926) saw a patient who was sixteen and a half months old, and

Schroeder (1922), one 20 months old. As Swift [66] noted, the cases of rheumatic fever in very young infants have almost all occurred in instances wherein the mother had the disease while the child was in utero; this suggests that both the susceptibility, and the infectious agent were transferred to the infant during pregnancy because, in general, other infants of rheumatic families do not give clinical evidence of the disease until after the fourth or fifth year of life. It is likely that during a considerable portion of this pre-rheumatic period the infant's tissues become so conditioned that they finally develop the capacity for showing true rheumatic lesions.

The youngest patient on record has been reported by Fischer [69]; the child was twelve and a half months old and died of rheumatic heart disease. The mother had active rheumatic fever from the third to the seventh month of pregnancy. The child developed fever, convulsions, otitis media, pneumonia and the typical picture of rheumatic valvulitis. Aschoff bodies were found at the necropsy. Fischer expressed the belief that the process was acute and probably did not date from birth although the child might have been stigmatized during fetal life.

Symptoms. The progress of the disease, as shown in new studies, conforms to the accepted pattern; major manifestations are sore throat, tonsillitis or infection of the upper part of the respiratory tract, fever, abdominal pains, arthritis, myositis, nodules, cutaneous eruptions, purpura, and carditis. Of 206 patients who had rheumatic heart disease, seen by Simmons,[58] 68 per cent gave definite histories of rheumatic fever; 19 per cent had had only recurrent tonsillitis; 4 per cent gave histories of chorea and 8 per cent had none of these. The first rheumatic attack occurred before the age of 20 years in 70 per cent of cases, before 30 years in 94 per cent. In nine cases symptoms did not develop until after the age of 50 years. As is well-known, and as has been emphasized again by Black,[70] the symptoms of the disease differ somewhat as they are seen in children and in adults. The latter generally present an acute onset, high fever, polyarthritis and drenching sweats. In children the symptoms are less definite: slow onset, frequently infection of the upper part of the respiratory tract, malaise, growing pains, fatigue, intermittent fever, rapid pulse without fever, night sweats, pallor, anemia, epistaxis, chorea, occasional nodules and frequently slight cardiac murmurs. Growing pains or chorea may be the only symptom.[67] Nodules, generally over knuckles, occur in 15 to 20 per cent of cases.[67, 70] According to Benjamin [67] rheumatic growing pains are characteristic: vague, dragging, fleeting pains in muscles, occasionally in joints, frequently accompanied by easy fatigability, loss of weight and anorexia.

[According to Shapiro (1935) rheumatic growing pains are more often in joints; nonrheumatic growing pains of children are more often in muscles.—Ed.]

Some of the 1200 children seen by Kaiser [65] had six or more symptoms; others, only a few. Pancarditis and nodules usually denote a serious form; tonsillitis, pallor and anorexia may indicate less serious rheumatism. Major

manifestations were present as follows: pancarditis in 64 per cent of cases, rheumatic fever with severe arthritis in 39 per cent, mild arthritis in 32 per cent, chorea in 29 per cent, muscular rheumatism (growing pains) in 18 per cent, pneumonitis in 3 per cent, erythema nodosum in 2 per cent, nodules in 1 per cent, pleurisy in 1 per cent and purpura in 0.4 per cent. Minor manifestations were present as follows: tonsillitis or sore throat in 43 per cent, fatigue in 36 per cent, anorexia in 34 per cent, pallor in 30 per cent, epistaxis in 15 per cent, cephalalgia in 6 per cent, abdominal pain in 5 per cent, cardiodynia in 4 per cent and nausea in 3 per cent. Chorea was not as frequently associated with carditis as was arthritis. Those patients who had mild arthritis or myositis had less carditis than those who had acute fever or severe arthritis. Tonsillitis or pharyngitis immediately preceded arthritis, chorea or endocarditis in 43 per cent of cases.

According to some [58] the disease, in general, behaves similarly in all latitudes, producing the same cardiovascular and other lesions. According to Schlesinger [71] the geographic variations are enormous; there is less carditis in the Netherlands than in England; more nodules in England than in America.

[In our last year's review, differences of opinion were noted as to whether the manifestations of the disease, when it occurs in the southern American states, are the same as those when it occurs in the north. The weight of evidence is in favor of geographic differences in symptoms: in the south the disease is milder; there is less arthritis for which reason the disease often goes undiagnosed.—Ed.]

Special Symptoms, Lesions, and Complications, with Pathologic Studies. Heart: Recent data confirm accepted ideas. Of Simmons' [58] 206 cases the mitral valve was involved alone in 83 per cent, the mitral with the aortic valve in 11 per cent; the aortic valve alone in 6 per cent. According to Cleland's [62] report on rheumatic carditis in 88 cases, it was found that mitral stenosis was more common in females than in males; aortic valvulitis more common in men. Evidence of unsuspected rheumatic carditis is often found at death in the bodies of persons who presumably were clinically unaffected by the disease. Of all patients dying at the Presbyterian Hospital, New York City, aside from those known to have had rheumatic fever, 1.2 per cent were found, by Hawking,[72] to have latent or active rheumatic carditis. The specificity of Aschoff bodies is doubted by some. Gross and Ehrlich [73] have made a contribution to the descriptive classification, life cycle, sites of predilection, and relation of the Aschoff body to the clinical course of the disease. They concluded that the myocardial Aschoff body is of a type specific for the myocardium and to be considered apart from other rheumatic lesions. Aschoff bodies pass through three stages. The earliest stage occurs up to the fourth week of the disease and presents small-cell coronal, and reticular, Aschoff bodies. The second phase occurs from the fourth to the thirteenth week and presents large-cell coronal, syncytial coronal, mosaic, and large irregular-cell polarized bodies. Polarized bodies occur

from the ninth to the sixteenth week; fibrillar bodies, after the thirteenth week. Aschoff bodies are found in 90 per cent of hearts of patients who die with evidence of active disease; in 59 per cent of those who die with evidence of old or recent activity.

It is generally believed that heart failure depends on myocardial rather than on endocardial damage, since degrees of the latter are not related to the occurrence or extent of cardiac failure. A study by Rothschild, Kugel and Gross [74] indicates that the severity of endocarditis bears no relation to the degree or age at onset of myocarditis and that rheumatic heart failure is related less to valvulitis, more to continued or recurrent myocarditis.

Blood vessels: Lesions in coronary arteries in rheumatic fever were described as being found in 56 cases by Karsner and Bayless,[75] and in four cases by Fraser.[76] In both articles specific lesions were described in detail; Karsner and Bayless also described vascular lesions not specific for the disease. There is a significant association between rheumatic heart disease and periarteritis nodosa (necrotizing arteritis) according to Friedberg and Gross [77] who reported four cases. An unusual case of portal obstruction, retroperitoneal varix and fatal hemoperitoneum, in the presence of rheumatic carditis and adherent periçardium, was seen by Feldman and Gross.[78] Easby [79] reported the appearance of spontaneous subarachnoid hemorrhage, possibly from a mycotic aneurysm, in a rheumatic child.

[The patient recovered; no pathologic data were given.—Ed.]

Renal lesions: Opinions differ as to the incidence of renal lesions in association with rheumatic fever. According to Blaisdell [80] a high percentage of rheumatic patients suffer from renal damage early in life. Of 2400 consecutive cases which came to necropsy, in 128 active or healed cardiac lesions were found. Of the latter group 38 subjects exhibited interstitial nephritis; half had been less than 40 years of age at death; a third, less than 30 years. The reported pathologic details in 16 such cases were related to small vascular structures, cortical arterioles and intralobular and arcuate arteries.

Pulmonary lesions: The pulmonary complications of rheumatic fever, according to Klein [81] include fibrinous pleurisy, pleurisy with effusion, atelectasis secondary to enlarged heart with pericardial effusion, vascular lesions of the pulmonary artery and its branches, and rheumatic pneumonitis. Symptoms of the latter may be evanescent, its course very variable, its characteristics hemorrhage and fibrinous exudate.

Cutaneous lesions; nodules and purpura: Nodules may be subcutaneous or cutaneous. Rosenberg [82] has reviewed their clinical differences and the histology of the latter; they vary from the size of a pinhead to that of a hazelnut, last for variable periods, and appear most commonly on the fingers, palms, and neck, also on the forehead, chest, and cheeks. In an epidemic in a hospital, observed by Chester and Schwartz [83] the predominant sign was crops of bluish, not tender, maculopapular, purpuric spots, chiefly on

the legs and arms, lasting one to six months and disappearing without scarring or desquamation. Holtz and Friedman [84] described an "unreported lesion": a hemorrhagic eruption confined to the mucosa of mouth and throat, seen rarely in examination of normal or nonrheumatic persons (occasionally in association with malnutrition, diabetes mellitus, vascular nephritis, and mumps), but especially in examination of patients in "the rheumatic state." It consists of one, two or a shower of circular, elevated, deep red spots, varying in size from that of a pinpoint to 2 mm. in diameter, looks like a fresh hemorrhage and fades in 24 hours, perhaps to reappear in different oral situations for as long as two weeks. The authors [84] expressed the belief that it is unrelated to purpura, and that it may be a non-embolic hemorrhagic enanthem. It does not exhibit the specific rheumatic lesions.

Abdominal symptoms and lesions: It is not generally realized that abdominal symptoms are not infrequent in cases of rheumatic fever and that on occasion they are marked, simulating appendicitis, too often leading to negative exploratory operations. Guptill [85] has given these symptoms consideration, describing details of eight cases (from a series of 160 cases of acute rheumatic fever) which simulated cases of acute appendicitis but in which inflammation of the appendix was not proved. Four patients were operated on; the appendices were normal. In Guptill's cases and in seven similar cases seen by Jones [63] the onset of the disease was manifested by fever, pain, nausea, and occasionally by vomiting. The pain was in the middle or lower part of the abdomen and was often lancinating. It subsided in two or three days in favor of characteristic polyarthritis. To distinguish it from appendicitis may be difficult. In rheumatic pseudo-appendicitis there is much less vomiting than in appendicitis, abdominal tenderness is present but muscular spasm is absent, and the leukocytes of the blood are increased in number without an increase in juvenile granular cells; the Schilling differential count is normal. In appendicitis, vomiting is almost universal among persons less than 20 years of age, and the Schilling differential count is abnormal, for there is an increase in juvenile cells. Careful inquiry concerning recent pharyngitis, arthralgia, carditis or previous rheumatism may prevent needless laparotomy. When in doubt it is safer to risk negative exploration of a rheumatic patient than to overlook possible appendicitis. Some writers believe such pseudo-appendiceal pain is referred from the pleura.

In two additional cases of Guptill, true suppurative appendicitis was proved at operation in the course of rheumatic fever. A few cases of true peritonitis attributable to this disease have been reported and probably are more common than is supposed. In one such case Rhea [86] noted plaque-like areas on the lateral and posterior peritoneal surfaces; the lesions were similar to Aschoff bodies. The intestines and mesentery were congested and edematous.

With periarteritis nodosa, abdominal symptoms may be notable. Ulceration of the intestine from arterial necrosis and occlusion often has pro-

duced diarrhea simulating that of ulcerative colitis. In two cases of periarteritis nodosa with rheumatic heart disease seen by Friedberg and Gross [77] abdominal symptoms dominated the clinical picture and led to exploration. These authors expressed the belief that such a complication may be the organic basis for some cases of "abdominal rheumatism."

[The diffuse hemorrhagic changes which, as noted in our last year's review, Collis believed were responsible for acute abdominal symptoms in three cases in which exploration was made are not mentioned in these various reports.—Ed.]

Laboratory Data: Sedimentation Rates, Blood Counts, Electrocardiograms. Blood counts of course should be made in cases of rheumatic fever. Lymphatic leukemia may occasionally simulate rheumatic fever.

[See later, herein, the note of a case described by Sutton and Bosworth; also, see notes on cases of aleukemic leukemia and leukopenic myeloid leukemia simulating rheumatic fever, in last year's review.—Ed.]

Previous opinions on the sedimentation rate have been confirmed.[55, 87, 88, 89] The rate is elevated in rheumatic fever and rheumatic carditis; it varies with the activity of the disease and affords one of the most delicate gauges of activity. It is normal in cases of uncomplicated chorea. However, it is elevated in cases of chorea with carditis, changes occurring even before the carditis is distinguishable. Because uncomplicated chorea is associated with a normal rate, Elghammer [88] suggested that it may not be a true rheumatic lesion, and Warner suggested that chorea is not an infective process although associated carditis is. According to Struthers and Bacal,[87] and to Perry,[89] the rate returns to normal or goes to less than normal with the onset of congestive cardiac failure with edema, a sign of bad import. Elghammer stated that when the rate increases after removal of foci of infection he suspects reactivation of infection.

Alterations in the rate in rheumatism result from a fall in the concentration of albumin in the blood, a rise in globulin, and alterations in the albumin-globulin ratio.[87]

Rheumatic children give no significant statistical variation from normal children, with regard to acidity and total chloride of gastric content, although the former exhibit greater variations on either side of mean values, according to Ogilvie.[90] The pH of the urine of rheumatic children is similar to that of normal or asthmatic children, even though the former show a higher excretion of various urinary acids.[91]

[This work does not seem to us to have been well controlled.—Ed.]

Values for blood lipids of children who have acute and chronic rheumatism were found by Kaiser and Gray [92] to be essentially the same as those of normal persons or of patients convalescing from scarlet fever, but the standard deviations were much greater for those who had the two diseases than for normal persons.

Electrocardiograms: Prolongation of the A–V conduction time and

alteration of rhythm are the best known electrocardiographic changes of acute rheumatic fever. Changes in the S–T segment and the T-wave are probably as characteristic and frequent, although they are not pathognomonic. Alterations reported by Easby and Roesler [93] and by Kohn [94] indicate that during the active stage the T-wave may be rounded and small, sometimes iso-electric, diphasic or inverted; and that during recovery it may become upright, tall and sharply peaked before returning to normal. In both reports it is noted that changes similar to those of coronary disease occur and it is suggested that they may result from alterations in coronary circulation, with consequent interference with myocardial blood supply.

Course of the Disease; Evidences of Activity or Reactivity. The average duration of the disease, according to Olesen,[61] is 17 years. Kaiser [65] studied the course of 564 children for three years. Within that time, 49 per cent had recrudescences, particularly those who had chorea. Within the first three years, 5 per cent died. Between the third and fifth years of the disease, 40 per cent had recurrences but only 1 per cent died. Within the first 10 years, 6 per cent died; 25 per cent had recurrences. After the first five years, the prognosis for ultimate recovery and freedom from recurrence is definitely improved. Of Simmons' 206 patients who had carditis, 17 per cent died; their average age was 33 years at death.[58]

Estimation of activity of the disease must always be made in absence of effects derived from salicylates or other antipyretic drugs. Evidences of continued or renewed activity include loss of weight, pallor, fever of low grade, abnormal pulse rate, fleeting muscular and joint pains, tonsillitis, epistaxis, abdominal symptoms, cutaneous lesions, increased cardiac force, transient pericardial friction, electrocardiographic alterations, leukocytosis and increased rates of sedimentation.[66, 95] Evidences of quiescence include steady gain in weight, slowing of pulse rate to normal, lack of extension of cardiac signs, absence of nodules or of chorea and fall in rate of sedimentation.[71]

Comparison of Rheumatic Fever with Tuberculosis and Atrophic Arthritis. Cecil again has reminded us of certain relationships between rheumatic fever and atrophic arthritis: both are prevalent in cold, damp climates and rare in the tropics; both progress with exacerbations and remissions; both attack joints and resemble chronic infections; both are associated with foci of infection, iritis, and nodules; both present proliferative and exudative granulomatous lesions—one involving chiefly the vascular system, the other, the joints, and, according to Cecil, both seem related to streptococci.

Similarities between rheumatic fever and tuberculosis have been pointed out for years. Recently (1932) Reitter and Löwenstein reported 70 per cent positive cultures for bacilli of tuberculosis in the blood of patients who had rheumatic fever. If the condition is related to tuberculosis, tuberculin reactions of rheumatic patients should be significant. Pascher [96] found no differences in the reactions of 245 rheumatic patients and 273 control subjects. Positive reactions were present in about 25 per cent of each group.

Etiology and Pathogenesis. Since conceptions of the etiology of rheumatic fever have not changed in any important particular from those outlined in detail in last year's review, we shall note current studies but briefly. The three chief theories continue to be (1) the microbic, (2) the metabolic and (3) the endocrine.

Microbic theory: The great majority of writers favor one of the variants of the bacterial theory: (1) the theory of bacteremia, (2) the theory of bacterial toxemia, (3) the theory of bacterial allergy. For each group, some hold responsible one bacterium, or its toxin or its antigen; others consider that any one of a number of bacteria, or their toxins or their antigens, may be causal. Highlights in pathogenesis are thought to be preceding tonsillitis or pharyngitis (generally with attendant hemolytic streptococci); a latent period of one to three weeks and then the attacks (fever, polyarthritis, and so forth).[97] The facts that sore throat so often precedes the initial or recurrent rheumatic attack, and that the disease, always one of low infectivity, occasionally assumes epidemic proportions, strengthen the bacterial theory.

Five varieties of microörganisms have been isolated from the blood of rheumatic patients: (1) a "sporulent" bacillus, anaerobic but facultatively aerobic; (2) a diplococcus, aerobic but facultatively anaerobic; (3) a streptococcus, generally hemolytic; (4) diphtheroid organisms (aerobic coccobacilli); (5) enterococci. Such is Bertrand's [98] grouping. Farah [99] listed about 25 organisms held responsible at one time or other. Hemolytic streptococci are currently the prevailing culprits, but the majority of writers have hesitated to ascribe more than contributory potentialities thereto, and believe infections therewith precipitate attacks in sensitized persons.[66, 100]

The bacteremic theory has been supported by Bertrand [98] who has isolated, from joints and in blood cultures, organisms which, in vitro, change from bacilliform types to diplococci; the cycle—bacillus, diplococcus, coccobacillus, streptococcus—could be developed in either direction. In monkeys inoculated intravenously with these organisms typical acute articular rheumatism developed: in 81 per cent of those inoculated with the bacillary form of the organism and in 52 per cent of those inoculated with the diplococcic form. It was concluded that in its virulent state the organism produces acute disease; in its attenuated form, it produces chronic disease. This organism, formerly called "Achalme's bacillus," is now called the "*diplostreptobacillus of rheumatism.*" According to Bertrand it is similar to the *Bacillus welchii.*

Howell and Burton [101] were unable to "dissociate" streptococci obtained from blood cultures of four patients who had rheumatic fever. The idea of dissociation, or mutation-forms, implies that each bacterium contains a virulent and an avirulent factor. It is believed that the virulent element, or form, of streptococci produces the smooth (S), and the avirulent, the

rough (R) colony. It might be of great clinical value to change the smooth, virulent strain into the rough, avirulent type. Two strains of nonhemolytic streptococci (*Streptococcus salivarius*), one of hemolytic streptococci (*Streptococcus pyogenes*) and one of *Streptococcus viridans* (*Streptococcus mitis*) were recovered in blood cultures. In spite of chemical and physical means, and passage through animals, the strains remained virulent, smooth, and stable for eight months. Howell and Burton concluded that there is little possibility of producing dissociation, a permanent change that occurs in a bacterium and then is transmitted to subsequent generations.

Farah [99] expressed the belief that the disease is attributable to pneumococci which inhabit the throat and are generally mistaken for streptococci. Intensive studies in a case of pneumococcus arthritis were used in evidence of this idea. We have already mentioned the idea of Reitter and Löwenstein (1932), that the bacillus of tuberculosis is the cause.

[Some of us have been unable to confirm the finding of tubercle bacillemia according to their method.—Ed.]

The chief proponents of the toxemic theory have been Birkhaug (1927) and Small.[102] Both have lately approved the allergic theory, as have many others.[90, 103]

[*Conclusions on Etiology.* It is obvious that the cause of the disease has not been established. The fact that so many different organisms have been isolated and are considered the cause of rheumatic fever suggests that probably no one of those so far isolated is responsible. Rheumatic fever is a fairly distinct disease entity. It would indeed be surprising were it found to be caused by many different organisms.—Ed.]

Special laboratory studies: No new studies on blood cultures and agglutination tests are reported. Eighty per cent of a series of 51 rheumatic children were skin-sensitive to hemolytic or nonhemolytic streptococci.[90] Numerous investigations on throat cultures and on the relationship to rheumatic attacks of infections of the upper part of the respiratory tract have been summarized by Pilot and Davis,[104] by Weinstein and Styron,[105] and by Bradley.[97] Not all epidemics of sore throat produce initial or subsequent attacks of rheumatic fever. Only a small percentage of patients who have pharyngitis acquire the disease, but those who do acquire it or who already have it seem peculiarly sensitive to nasopharyngeal organisms, chiefly of the hemolytic streptococcal variety. The *Streptococcus epidemicus* (a hemolytic streptococcus) seemed the major invader to Pilot and Davis.[104] Weinstein and Styron [105] made 727 throat cultures of 261 patients (101 patients had rheumatic disease; 160 were controls). Green-producing streptococci were present in all throats, and indifferent streptococci in most. Hemolytic streptococci were found in examination of 43 per cent of the patients who had rheumatic disease and in examination of 31 per cent of the control subjects, and were equally abundant in both. Although the pharyngeal flora of the rheumatic patients was essentially the

same as that of the control subjects, exacerbations of the disease bore a definite relationship to the presence of hemolytic streptococci.

Todd (1932) found in blood serum a substance (antistreptolysin; antihemolysin) capable of neutralizing the hemolytic substance formed in vitro by hemolytic streptococci. After any infection with hemolytic streptococci, the antihemolysin titer of serum rises materially. Increases were almost always found by him after an attack of acute rheumatic fever, a point in favor of a connection between the disease and hemolytic streptococci. The normal limit was thought to be 50 units. Coburn and Pauli (1932) agreed with these conclusions. Griffiths [106] found high titers (more than 50 units) in work with the serum of the majority of patients, who had subacute rheumatism, infective arthritis, spondylitis, or fibrositis, but generally the titer was normal in cases of spondylitis osteo-arthritica or in cases of osteo-arthritis. This suggests "an association between rheumatic disease and hemolytic streptococci that cannot be ignored." Much higher titers (more than 200 or 300 units) were found in working with the serum of normal persons by Myers and Keefer,[107] and by Wilson, Wheeler and Leask.[108] The former agreed that in the majority of cases of rheumatic fever high titers are found, but states that in 21 per cent of them titers were no higher than those seen among normal persons. Furthermore, according to Myers and Keefer,[107] titers of the serum of patients who have atrophic and other forms of arthritis are normal. Wilson, Wheeler and Leask [108] found about the same very wide range of variation in both rheumatic and nonrheumatic patients, and concluded that the results are of no etiologic significance. Titers bore no relationship to the presence of agglutinins and were not related to results of cutaneous sensitization tests.[107]

Fibrin of man is normally completely liquefied by filtrates of hemolytic streptococci (Tillett and Garner, 1933). The fibrin of patients recently recovered from hemolytic streptococcal infections is resistant to such lysis. Resistance to fibrinolysis is apparently attributable to production of anti-fibrinolysin and bears a close analogy to the production of antihemolytic antibody. Hadfield, Magee and Perry [109] have noted that patients who have a rheumatic relapse frequently demonstrate total resistance to lysis.

Other theories of etiology: The year's literature affords little support for other than the theory of infection. The metabolic theory was favored by Warner.[55] At least, Warner expressed the belief that many of the manifestations of the disease (not carditis) are due to causes other than infection, presumably an "altered underlying biochemical state" resulting from dietetic deficiency or imbalance. Rheumatic patients tend to eat too much carbohydrate; too little fat. Dietary correction lowers the tendency to the disease. Llewellyn's [55] discussion of his ideas along these lines is interesting but highly theoretical.

That rheumatic fever may result from the combined influence of vitamin deficiency plus infection, and from neither factor alone, was the thesis of Rinehart, Connor, and Mettier.[110] Guinea pigs subjected to experimental

scurvy (deficiency of vitamin C), and then to superimposed infection, acquired cardiac, articular and other lesions markedly resembling those of rheumatic fever. Minor changes only were induced by either the diet or infection alone. Perhaps latent scurvy of man provides the rheumatic diathesis, conditioning patients to later precipitating infections.

[In a recent discussion on this work it was agreed that changes could be induced, but some workers felt that the changes were probably scorbutic, not rheumatic.—Ed.]

The combination of experimental deficiency of vitamin A and infection did not produce significant lesions at the hands of Stimson, Hedley and Rose,[111] but with other dietary deficiencies certain valvular lesions were produced in a few animals. Lesions similar to Rinehart's experimental myocardial lesions in scorbutic guinea pigs were produced by injections of streptococcal exotoxin, without introducing live microörganisms.

Treatment. The value of established methods has been reaffirmed; no new treatments were proposed.

Drugs: We are again reminded that salicylates are helpful in reducing fever and pain but that they do not prevent or alter cardiac complications.[95, 112] Fantus [113] advocated amidopyrine when salicylates fail or are not tolerated. Jenkins [103] expressed the belief that the use of atropine hypodermically is more efficient than salicylates in reducing fever and joint-distress but that it is equally as useless as salicylates for a real cure. The dangers of cinchophen have been overstressed, according to Lawler [114] who expressed himself as in favor of the use of mono-iodocinchophen. No relief was received by six patients whom Slot and Deville [115] treated with gold (solganol). Untoward reactions may occur therefrom: nephritis and jaundice. Injections of histamine were given by Shanson and Eastwood [116] to patients who had subacute rheumatism; moderate relief was noted.

Tonsillectomy: The controversy regarding the value of tonsillectomy has continued. The majority of observers favored it. Thus Miller [117] expressed the belief that it gives the best chance of safeguarding rheumatic children from the more serious forms of the disease. According to Swift, among nonrheumatic persons, five to 30 years old, who have tonsillitis or pharyngitis, only about 10 per cent may be expected to suffer from definite rheumatic fever, but among those of that age who have previously had rheumatic fever, at least 50 to 60 per cent who acquire infections of the throat will have a new attack of rheumatic fever. Thus the importance of tonsillectomy in safeguarding such patients is obvious. The opinions of Kaiser [65] are well known: subsequent attacks of rheumatic fever occur slightly more often among children whose tonsils have not been removed at the initial attack. The mortality rate is nearly 50 per cent less among those whose tonsils have been removed before the initial attack. Tonsillitis or sore throat preceded rheumatic fever in 59 per cent of children studied. Although tonsillectomy lessens the mortality and the incidence of the more serious rheumatic manifestations, it does not prevent recurrences. The

views expressed by Coates and Gordon [118] were similar. Stahr [119] noted no ill effects, but often much benefit, from early tonsillectomy.

Wholesale tonsillectomy is useless, according to Schlesinger [71] and to Poynton,[120] for pharyngitis affecting a tonsillectomized child can cause rheumatic fever. The tonsils should be removed, however, if they are septic or markedly enlarged, or if the child has repeated attacks of sore throat.

Diet: Poynton [120] has not noted the reputed dislike of rheumatic children for fat. A diet such as is given in the presence of any febrile disease seemed indicated to Douthwaite [121] but in spite of cellular destruction and loss of nitrogen from fever, he advised not to increase the intake of proteins lest indigestion ensue. For the sickly child an increase in calories may be most helpful.[70]

Rest: The value of prolonged rest was stressed by all writers.

Vaccines, antigens, serums: Contrary to the opinion of many, Wolffe [95] and Cecil [56] expressed the belief that streptococcal vaccines are of value in treatment and prophylaxis. Injections of bacterial antigen of *Streptococcus cardio-arthritidis,* in smaller doses than any yet used in biologic therapy, are definitely helpful, according to Small.[102] The antigen is diluted to an extent which at first appears to be an absurdity, but control studies convinced Small of their potency and usefulness. Overdosage is followed by prompt exacerbations of rheumatic fever. A discussion of the various reactions to treatment and a detailed plan of dosage are given in the article. In general, the use of foreign proteins is unsatisfactory but occasionally, in obstinate cases, it gives startling results, and stops the acute attack speedily.[70, 113]

[Some may have a remission shortly thereafter, however.—Ed.]

In 12 cases results with streptococcus (scarlatina) antitoxin were encouraging.[112]

Climate and institutional care: Convalescent homes constitute one of the greatest advances in the therapy of this disease.[61, 71] A prolonged sojourn in a subtropical climate may be a "specific." Eleven of 14 patients who had active carditis and who were sent by Nichol [57] to Miami improved markedly or went into a remission. Roche and Jones [122] sent to Florida 14 children who had been affected with severe carditis for an average of four years; 12 of them were conspicuously improved. Even after they had returned to New England improvement continued.

Effect of pregnancy: From a study of 40 males (as controls), 28 nulliparous women and 41 parous women who had carditis, Gilchrist and Murray-Lyon [123] were unable to show that two pregnancies shortened the life of the rheumatic patient. One or two children may generally be borne without detriment. Similar conclusions were reached by Scott and Henderson [124]; the physical strain of pregnancy can be minimized or counteracted by sufficient rest. If the patient has the means to obtain rest, one or two pregnancies may be permitted. However, repeated pregnancies are not well borne and may provoke fatal cardiac decompensation.

Prophylaxis: Prevention of relapses is more likely under the following regimen[71, 113]: a nutritious diet high in vitamins; cod liver oil; tonsillectomy; outdoor life with graded exercises; avoidance of chilling and, above all, of respiratory infections. If the latter are epidemic, avoidance of chilling and of crowds; spacing of beds; isolation from patients who have colds; sterilization of the patient's plates, cutlery, and pencils; concentrated treatment with acetylsalicylic acid for three weeks after an infection of the throat, and a stay in a warm room during such an infection, are indicated. Institutional care or life in a subtropical climate is most helpful in certain cases.

Sydenham's Chorea

It was accepted by Mutch[125] and by Copeman[126] that Sydenham's chorea is related to rheumatic infection, as is indicated by the occurrence of cardiac sequelae in 30 to 40 per cent of cases of chorea. Nervous strain and deficiency of calcium may also be factors.[125] However, since the sedimentation rates are generally normal in cases of chorea not accompanied by carditis, some investigators[55] have expressed the belief that the condition may not be infective, although complicating carditis probably is. The average duration of the disease is about 27 days in mild cases, 44 days in moderately severe cases and 62 days in severe cases.[125, 127] Copeman expressed the belief that it lasts more nearly three months than six to ten weeks as generally is stated.

Treatment. The therapy of the past was outlined by Mutch.[125] Three newer contributions to the therapy of chorea are the use of the sodium salt of phenyl-ethyl-hydantoin (nirvanol), of ketogenic diets, and of typhoid-paratyphoid vaccine. Mutch and others got little result with diet. It has been noted repeatedly that patients who have chorea have been benefited by intercurrent fever (Turnovszky, 1930) and that measures which help most in chorea are accompanied by fever. Various methods of fever therapy have accordingly been advocated: the use of nirvanol (Roeder, 1919), autoserum (Brown, Smith, Phillips, 1919), chemical protein (Horton, 1922), fever reactions with milk (von Kern, 1923; Hymanson, 1926), *Treponema hispanicum* (Mas de Ayala, 1930), typhoid-paratyphoid vaccine (Sutton, 1931; Trawley, Pepper and Wathe, 1932; Bateman, 1933).

[More recently, fever machines and colloidal sulphur have been employed. Reports on these belong in our next review.—Ed.]

Nirvanol: The usual nirvanol reaction includes drowsiness, headache, fever, rash, eosinophilia and leukopenia; the fever presumably is the useful component. Untoward reactions may occur: purpura, jaundice, diarrhea, nephritis, incontinence of urine, enlargement of the spleen and liver, prolonged high fever, coma and occasionally death.[125, 128] Of 28 cases in which Silber and Epstein[129] administered treatment, in 10 improvement was prompt, choreiform movements stopping completely. In 18 there was no improvement; in nine of these cases the reaction failed to develop. Asso-

ciated carditis is not affected by the treatment. Marick[130] noted improvement in the majority of 55 cases in which treatment was given. However, two to three years later some of the patients had recurrences; others, dyspnea; many were still nervous. Recurrences therefore apparently are not prevented by nirvanol. Its value was accepted by Call[131] with reservations. Of 26 patients, 18 were markedly improved in 10 days; five became free of symptoms in 20 days. In one case, adenitis, ulcerative stomatitis and gingivitis, and ulcerative conjunctivitis developed but the patient recovered. In spite of these and other favorable reports (Pilcher and Gerstenberger, 1930), the Council on Pharmacy and Chemistry of the American Medical Association has not seen fit to accept the drug (1932). Mutch[125] expressed the belief that the use of nirvanol is dangerous; Copeman[126] found it of little value. Don[128] stated his belief that generally it can be given with confidence; however, he noted prolonged, persistent fever in one case.

Typhoid-paratyphoid vaccine: The advantages of febrile reactions produced by vaccine were first reported by Sutton (1931). A second report[127] concerned 150 patients so treated and 150 patients treated otherwise. By inducing fever with the vaccine, the duration of mild cases was shortened (as compared with those treated otherwise) from 27 to six days; moderate cases, from 44 to nine days; severe cases, from 62 to 16 days. The average number of treatments required was six (from three to 18); they were usually given daily. In only 10 per cent of cases was the result disappointing. No untoward reactions were encountered. Active carditis was not a contraindication; indeed, it seemed to be benefited. Capper and Bauer[132] induced 297 reactions in 23 cases (generally in series of one each day for one week). The disease in these cases had lasted from four months to four and a half years. Marked improvement in some, and, in several, prompt cures were obtained and were maintained many months. Equally impressive results were obtained by Fish[133] and by Redfearn[134] in one case each, and by Hoverson[135] in two cases. Hoverson also treated four patients who had Huntington's chorea; two completely recovered, two were unrelieved.

Comparing the results from the use of typhoid vaccine (23 cases) with those obtained with nirvanol (24 cases), Montfort[136] strongly favored the former on the grounds that it shortens the course of the disease, is harmless, is followed by a significant lack of recurrences and sequelae, and is easy to administer. With nirvanol, which was definitely helpful, the disease lasted an average of 24 days; with vaccine, 16 days. Marick on the other hand felt that each was helpful but that nirvanol was safer.

Other medicines: Believing that a disturbance of calcium metabolism occurs with chorea, Mutch[125] prescribed calcium-acetylsalicylic acid, 60 grains (4 gm.) daily. The nervous manifestations were controlled after an average of 17 days (7 to 46 days).

Chronic Arthritis

Introduction and Terminology. Because of its frequency and the chronic disability which it produces, chronic arthritis in conjunction with fibrositis has an enormous morbidity rate. The economic importance of this disease is greater than that of tuberculosis, heart disease and cancer combined.[2, 4] When the term "chronic arthritis" is used, it generally refers to "atrophic arthritis" or "hypertrophic arthritis" or to both forms undifferentiated; all other forms of chronic arthritis such as tuberculous, gonorrheal, traumatic, or gouty arthritis are, or should be, tacitly excluded. In this review, regardless of the terms used by authors quoted, we shall use the nomenclature adopted by the American Committee,[137] according to which "atrophic arthritis" is employed as synonymous with "chronic infectious," "proliferative," "type one," "synovial" and "rheumatoid arthritis"; and "hypertrophic arthritis" as synonymous with "chronic senescent," "degenerative," "type two," "chondro-osseous arthritis" or "osteo-arthritis." Terms approved by the committee as a group are not necessarily those individually preferred by members of the committee or by the editors of this review. It is assumed that the reader is familiar with the basis of these terms and with the various criticisms thereof.[4, 137, 138, 139] Each term has its merits and its demerits. Under certain circumstances a pathologic term may be preferable, under other conditions a clinical term seems best; it is important for the reader to recognize their synonymity.

Etiology; General Remarks. Current reports continue the arguments as to the relationship between the two great types. The majority of authors feel that the two are so different in clinical, chemical, roentgenologic, and pathologic manifestations, as well as in prognosis, that they must be considered separately and must represent two distinct diseases. Others believe that the two are merely different manifestations of the same fundamental disturbance and that their obvious differences arise merely from the factors of the patient's age at the time of onset of the disease, of his physique (asthenic or hypersthenic constitution) or because of differences in the reactions of various individuals to the same insult. Still others believe that the so-called differences are more imaginary than real, and that there is but one type which may, however, arise from one or several causes. Regardless of whether the two types have a common etiology, the great majority of writers insist that clinically they are sharply distinct.

Strictly speaking nobody, of course, confines himself to a belief in one solitary cause. All recognize the interdependence of seed and soil, but opinions differ as to whether abnormality of the seed or of the soil is the more important, and as to what is the essential cause without which, regardless of the presence or absence of contributory or precipitating factors, the disease could not eventuate. At times the contention simulates the one on the priority of the hen or the egg. Those who favor the theory of infection ascribe primacy to the seed and believe that a microörganism is the essential cause,

although admitting the need for a proper soil. Those who favor the "metabolic theory" generally admit the secondary importance of focal or other infection but lay stress on physiologic alterations which prepare the soil for various bacteria to produce arthritis. The two viewpoints are by no means as antagonistic as some would believe. The adherents of each are probably but facing each other, perhaps at times a bit angrily, through the same window.

Those who favor the idea of separate types and of the probability of a separate cause for each type are too numerous to mention but include, in this country, Bauer, Boots, Dawson, Cecil, Ghrist, Hall, Hench, Holbrook, Key, Miller and many others.

Those who favor the clinical separation of the two types but believe that both may have the same cause, or very closely allied causes include, in this country, Fletcher, Osgood, Pemberton, White and many others. Adamson[6] expressed his viewpoint thus: "As champagne or port wine will do nothing to one person, give another gout, and give a third a headache, so streptococci on a soil previously prepared by intestinal toxemia may produce rheumatoid (atrophic) arthritis in one, (hypertrophic) osteo-arthritis in another, fibrositis in a third, one of the differences being not in the bacterial invasion but in the physico-chemical or 'electro-chemical' state of the tissues."

[The analogy is interesting but is worthy of criticism. Nobody believes that champagne and wine are causes of gout. They merely act as one of many widely different predisposing or precipitating factors. Much confusion is fostered by such statements in which writers do not assiduously differentiate in their papers, or even in their own minds, between what are merely inciting or predisposing factors and what should be considered the actual etiologic factor, the sine qua non. Were the numerous secondary factors in the production of the chronic arthritides not so often thoughtlessly or carelessly raised to the status of prime cause, there would not be so many theories and variants thereof to pester us.—Ed.]

R. and J. Kovacs[140] argued that a streptococcal infection of low grade is present in both types of arthritis; the type resulting depends on the patient's constitutional configuration—atrophic arthritis in the asthenic, hypertrophic in the sthenic type. Sherwood's[141] therapy is based on the idea that both, and also the menopausal type, are of infectious origin.

[No proof is offered regarding etiology. "Menopausal arthritis" is not a clearly defined entity.—Ed.]

Brooks[142] expressed the belief that both are infectious but that atrophic arthritis is probably streptococcal, hypertrophic arthritis staphylococcal, in origin.

[This is the exact opposite of Crowe's ideas, 1930.—Ed.]

According to Haden[143] the fundamental factor in both types is probably a disturbance in capillary circulation. Elsewhere, however, Haden[144, 145]

has seemed to favor the theory that any one of a number of different causes may produce either type of arthritis.

Those who would reunite the two types under one heading, and who favor a unity of causation, include Archer, Burbank, Clawson and Wetherby, Knaggs, Willcox, and Wright. According to Archer [146] the (unstated) cause of both may be the same, since, in a somewhat analogous manner, syphilis can cause either a proliferative (syphilitic) arthritis or a degenerative arthritis of the Charcot type. Wetherby [147] was unable definitely to segregate atrophic or hypertrophic arthritis or even rheumatic fever one from another because of the clinical, humoral, radiologic, and pathologic similarities which he found they exhibited. He expressed the belief that all are probably streptococcal. In his opinion chronic arthritis may often result from an acute attack indistinguishable from rheumatic fever.

[Shapiro,[148] in the same city, studying "several hundred cases" of rheumatic fever from childhood to adulthood, found no instance wherein chronic arthritis directly followed rheumatic fever.—Ed.]

Burbank [149] expressed the view that chronic arthritis is caused by an infection; the chief offenders are streptococci, not of a specific strain, together with a variable, "X." The latter factor may be dietary defect, endocrine abnormality, sensitization, depletion from some intercurrent cause, mental and physical trauma, faulty posture, or some other abnormality. While infection may play a rôle in each type of chronic arthritis, a nutritional change, probably a vitamin deficiency, is the fundamental cause of both, according to Wright [150]; the difference mainly arises from the variable reactions of different people.

[Again no proof whatever is offered.—Ed.]

The idea of one clinical type produced by various causes is again advocated by Nissen,[151] Nissen and Spencer,[152] and Ober.[153] Accepting the concept that chronic arthritis is one disease, Nissen expresses the belief that variations are a matter of individual reaction and that the very multiplicity of functional disturbances points definitely to the conclusion that there may be no one etiologic agent. With this Ober agrees, although elsewhere he and Burnett [154] have suggested that "non-specific arthritis" is a deficiency disease.

[Data given do not permit this conclusion. True arthritic changes, as contrasted to scorbutic changes, have never been clearly demonstrated in animals on diets variously deficient.—Ed.]

Arthritis is not a disease, per se, according to Wolf,[155] but a symptom—an expression of an inflammatory reaction to an infinite number of factors.

[The editors cannot but feel that, regardless of etiology, the two diseases are separate and not merely different manifestations of the same process among persons of different age groups. Classical atrophic arthritis frequently is seen just appearing when patients have passed the age of 50, 60 or 70 years. Atrophic arthritis at this

stage is essentially the same as it is at the age of 20 years. Conversely, not infrequently one sees cases of premature senescent arthritis—typical hypertrophic arthritis with Heberden's nodes—affecting a woman 30 to 35 years of age. Thus, too, rheumatic fever occasionally may first appear in a person past 50 years of age. Although minor variations appear in adult rheumatism as compared to juvenile rheumatism, the two chief characteristics of the disease, carditis (not endocarditis) and articular resolution without chronic arthritis, are manifest in both groups, regardless of age. It is admitted that the patient's tissue-age and chronologic age are not necessarily identical but it seems apparent that, regardless of age at onset, the two diseases tenaciously retain their distinct identity too often for us to accept the idea that the varying clinical expression of arthritis is conditioned by age only, either tissue-age or chronologic age. It is understood, of course, that the editors recognize the differences between clinical hypertrophic arthritis, one disease, and radiologic hypertrophic arthritis, several diseases.—Ed.]

The terminology favored by individual writers depends of course on their ideas on etiology. If they are sufficiently convinced of the bacterial causation, they call the condition "infectious arthritis"; otherwise they rely on less committal terms based on pathologic, radiologic or clinical differences. Brooks [142] subdivided streptococcal rheumatic disease on anatomic grounds into types affecting various tissues such as mucous, dermal, connective, fatty, muscular, cardiac, nervous, glandular, ocular, otic, and articular tissues. Others also (Fisher, 1929) have subdivided "chronic arthritis" into synovial (atrophic) arthritis, or chondro-osseous (hypertrophic) arthritis. Another writer [156] has proposed a numerical and alphabetical system as a simplified means of recording the various etiologic factors: allergy, bacteria, climate, diet, endocrine abnormalities, fatigue, gastrointestinal disturbances, trauma, nervousness. The unknown factor, "*X*," is the soil. If "*B*" signifies bacteria, "*E*" endocrinopathy, "*N*" nervous disturbance, and "*T*" trauma, and the patient has such abnormalities, his formula reads: Patient $= X\ (B + E + N + T)$.

[Such a "simplified" concept seems more ingenious than practical.—Ed.]

Distinctions between the Two Types: Clinical, Pathologic, and Radiologic

The accepted distinctions between the two types were outlined fully in the first review [4] and in the Primer [137] and will not be repeated here. Gelber and Goldberg [10] reviewed the usual roentgenologic differences, using Goldthwait's [157] classification, in which rheumatoid arthritis is subdivided into "infectious arthritis" and "atrophic arthritis."

[Here as elsewhere the roentgenologic subdivision seems not clear, and unnecessary.—Ed.]

Various roentgenographic alterations are common to all types of arthritis, according to Taylor, Ferguson and Kasabach,[158] and there is no one diagnostic feature in any. However, each type has a characteristic combination of alterations that makes a roentgenogram valuable in diagnosis.

To venture a clinical or etiologic diagnosis, the roentgenologist should at least be told the duration of the disease. The roentgenogram in a case of fairly early gonorrheal destructive arthritis may simulate that of late tuberculous destructive arthritis. In roentgenograms, atrophic and hypertrophic arthritis appear to be distinct entities. Both may affect the same joint; even so, the characteristics of each type are generally demonstrable. The constancy of the findings in cases of atrophic arthritis does not favor further subdivision of this group.

Atrophic (Infectious, Proliferative, Rheumatoid) Arthritis

Symptoms and Course. In some cases the onset is abrupt, with an acute, febrile reaction, considerable articular heat, redness, swelling and other constitutional signs of infection; this subtype is often distinguished from the more chronic variety and has been called "subtype a" by Holbrook,[159] "group one" by Cox and Hill,[160] "secondary rheumatoid arthritis" by Buckley [161] and "infectious arthritis" by Senturia.[162] This variety of the disease is generally attributed to infection. Foci of infection are usually to be found and their removal may cause prompt and notable improvement, with early cessation, instead of an indefinite, smouldering progression of the disease.

In the majority of cases, however, the onset is insidious and relatively afebrile, joints are affected somewhat symmetrically, foci of infection either are not found or their removal gives little relief. This major variety has been called by various authors "subtype b," [159] "group two," [160] "primary rheumatoid arthritis," [161] and "atrophic arthritis." [162]

Usual symptoms of the disease need not be listed again here.[4] Wetherby again has reported his analysis of 350 cases (1932 and 1934 [147]) of chronic arthritis but since cases of both types were indiscriminately included, the analysis does not lend itself to comparison with others.

[Even though an author believes in unity of cause, for the sake of comparative statistics he should include a clinical differentiation; otherwise his data are practically useless.—Ed.]

Acute rheumatoid (atrophic) arthritis and Still's disease are one and the same, according to Moltke [163] who reported four cases of the former (adult Still's disease) in males, aged 15 to 28 years. Common characteristics were subacute, sometimes remitting, fever, peri-arthritis with fusiform swelling, poly-adenitis (in 37 per cent of a larger group of cases of atrophic arthritis), anemia, muscular atrophy, sweats, increased rate of sedimentation, and chronicity. Splenomegaly is not a requisite for Still's disease; it was absent in three of Still's 10 cases. Serositis of the pericardium, pleura, and peritoneum are variably present in Still's disease; they are rarely found in atrophic arthritis. Splenomegaly in cases of juvenile Still's disease represents a physiologic response more common in children than in adults.

Of four cases of *scleromalacia perforans* (various-sized holes in sclera without dominant signs of inflammation) reported by van der Hoeve,[164] in three the patients were women who had advanced atrophic arthritis. Perhaps both affections have a common cause.

Nissen [151] and Nissen and Spencer [152] expressed the belief that "individual reactions" rather than factors of heredity, environment, focal infection, worry, age of onset, severity or duration of arthritis, or treatment determine the prognosis. Following the course of 95 patients with different types of arthritis to their deaths, these authors found that four life courses were graphed regardless of the type of arthritis present. Course A is that of the patient who, with the onset of arthritis, drops to some lower level of activity. He remains there for a time, and then, because of better tissue inheritance, determination, successful therapy, or natural individualistic reaction, he climbs back to the former level of activity and remains there for the rest of his life. The average duration of life after the onset of the disease was 27 years. In course B the patient, after his initial attack, experiences remissions and relapses, the latter increasing in duration and frequency; the mean course is a slow, steady decline. The average duration of life after the onset was 17.3 years. In course C the patient progresses until he receives a severe systemic upset, perhaps an infection, then rapidly polyarticular destruction develops, at which level of crippledom he may remain, with little variation in his arthritis; he may survive long at a minimal level of function. The average duration of life after onset was 19 years. In course D the disease develops acutely or insidiously; it progresses with variable rapidity, the life course dropping steadily to death; in such cases surgical measures may be dangerous. The average duration of life after onset was seven years.

[Such figures as the authors gave, mixing various types of arthritis—atrophic, hypertrophic, mixed types, gonorrheal, tuberculous and rheumatic fever—all together are unfortunately of little value. It might be said that a patient who has almost any chronic disease, regardless of all other factors, will (*a*) soon get well, (*b*) slowly get worse but not die, (*c*) rapidly get worse but not die, or (*d*) die fairly soon. After all, there are no other possibilities. However, such few statistics as the authors gave on the course of the separate types represent valuable information. The authors must have some very useful information were it restated.—Ed.]

Of 27 patients who had atrophic arthritis (type I) 4 per cent (one case) followed life-course A, 36 per cent (10 cases) course B, 30 per cent (eight cases) course C and 30 per cent (eight cases) course D. In comparison, 3 per cent (one case) of 30 patients who had hypertrophic arthritis (type II) followed course A, 70 per cent (23 cases) course B, none course C, and 20 per cent (six cases) course D.

[This statement is not clear. It implies that in certain cases hypertrophic arthritis leads to fairly rapid death, an untenable idea.—Ed.]

Of 26 cases of mixed (atrophic and hypertrophic) arthritis, 12 per cent (three cases) followed course A, 46 per cent (12 cases) course B, 15 per cent (four cases) course C, and 27 per cent (seven cases) course D. Of eight cases of Strümpell-Marie's disease (atrophic spondylitis) 80 per cent (five cases) followed course B and 20 per cent (three cases) course D.

The effect of intercurrent disease (tuberculosis, syphilis, pernicious anemia, gout, psoriasis, diabetes, and hyperthyroidism) on the course of atrophic arthritis was discussed by Cecil [165] who expressed the belief that atrophic arthritis rarely but occasionally occurs in association with tuberculosis; he gave examples of the coincidence of arthritis with the diseases mentioned.

Pathology. The pathologic distinction between atrophic and hypertrophic arthritis has been fully given [4, 137, 138, 139] and has been reviewed by Pemberton and Bach.[166] No new work was presented.

Routine Laboratory Data. In atrophic arthritis (18 cases) according to Steinberg [167] the average leukocyte count is higher than it is in hypertrophic arthritis (26 cases); in the former there is a definite tendency for the Schilling differential count to shift to the left. This fact may be helpful in differentiation. Persistent eosinophilia of 5 to 8 per cent may occur in severe cases. As does the sedimentation rate, so does the nuclear count in atrophic arthritis reflect the severity of the disease to a great extent and together with the rate of sedimentation, the nuclear count can be used as an index of activity, according to Rawls, Gruskin, Ressa and Jordon [168] who studied 263 determinations of the rate of sedimentation and 258 nuclear counts in 50 cases. The value of the rate of sedimentation has been similarly confirmed by Stainsby and Nicholls [169] who, using the corrected sedimentation index of Rourke and Ernstene, noted that the average rate increases with the patient's age and tends to be lower in summer than in winter. Changes in the agglutinin titer for hemolytic streptococci appear and develop slowly; they are not related to the activity of the disease and no correlation between them and the sedimentation rate exists. A method of determining the sedimentation rate with blood obtained from a pricked finger, without venipuncture, was described by McSweeney.[170]

Degenerative diseases are more likely to be associated with hypercholesteremia than are inflammatory diseases, which are often associated with hypocholesteremia. Some significance may be attached, therefore, to the finding by Bruger and Poindexter [171] that in seven cases of hypertrophic arthritis the concentration of plasma cholesterol was higher (178 to 441 mg. per 100 c.c.) than it was in three cases of atrophic arthritis (168 to 229 mg. per 100 c.c.). These findings were confirmed in the larger series of Hartung, Greene and Bruger [172] (33 cases of atrophic; 59, of hypertrophic arthritis). The concentration of serum calcium in atrophic arthritis is essentially normal; in hypertrophic arthritis it is slightly but significantly increased, an increase not attributable to age.[172]

Etiology and Pathogenesis. In general the year's literature presents no

significant modifications of the outline and schemes given in last year's review. Current theories remain: (1) that of infection with the three variants, (*a*) bacteremia, (*b*) bacterial toxemia, and (*c*) bacterial allergy; (2) that of metabolic abnormality with its numerous variants such as the ideas of (*a*) deranged metabolism of carbohydrates, (*b*) deranged metabolism of protein, (*c*) deranged metabolism of sulphur, (*d*) food allergy, and (*e*) vitamin deficiency; (3) the theory that circulatory imbalance or deficiency leads to articular "blood hunger" and consequent arthritis, and (4) the theory of endocrine abnormality. Writing on the etiology and pathogenesis of arthritis, investigators in the past have, of course, recognized the interrelationship of three factors: (1) the predisposing factor, soil, (2) the true or fundamental etiologic factor, generally thought to be a microorganism, and (3) the precipitating factor, such as shock, grief, nervous fatigue, endocrine crisis and so forth. Thus, there has been formed the useful equation of the causal factor as the numerator, and the person's resistance (soil) as the denominator. When the value of the denominator is equal to, or greater than, that of the numerator, arthritis does not occur, regardless of foci of infection and so forth. When the balance is upset by an increase in the numerator (added infection) or by a decrease in the denominator (a change in the patient's resistance making the soil proper for the development of the disease, the soil perhaps altered as a result of some precipitating factor) then arthritis may occur. Tacitly admitting the importance of all these factors of the equation, writers, nevertheless, have been inclined to stress sharply the overwhelming importance of the seed—the fundamental factor without which arthritis cannot develop regardless of soil, precipitating factors or other factors. In articles of the past, the tendency was for the author to state rather boldly what he believed the main cause of the disease to be, whether infection, metabolic abnormality, endocrine disturbance, or neurogenic disorders, and for the author to give but little recognition to the arguments of others.

In current literature a subtle change is evident. It is rare now to read the blunt statement "a germ is responsible" or "circulatory derangements are the cause." Now, while still defending the claims of their favorite causal factor, writers are admitting the significance of other factors. Speaking with less assurance on their favorite theme, they are careful to erect a small monument to the unknown god of others. They resemble the roulette player, who, after carefully placing his chips, tosses a precautionary one on the 0 or double 0 just before the "rien ne va plus." Thus splitting their ticket, they are taking the best from each theory to support the eclectic theory that there is probably no one cause for the disease and that any one of a number of causes may be responsible.[148, 173]

This indicates a growing tolerance, perhaps a broadening of vision, but it has not yet led to increased clarity of ideas, rather the opposite. For during this stage of transition the literature has become less clear, ideas are less concise and it becomes increasingly difficult to catalogue a writer. One phy-

sician wrote: "There is no one cause for chronic non-specific arthritis of either type. Perhaps most cases result from the interaction of several factors. . . . It is quite probable that a disturbed circulation is often the primary disturbance."[144] But elsewhere[143] he wrote, "There is not one cause for chronic rheumatism. Perhaps most cases result from the interplay of several factors. . . . Infection is the most important factor in the atrophic type." And again,[145] "Possibly the disease (atrophic arthritis) cannot develop in the absence of bacteria but the presence of bacteria alone is insufficient in most cases to produce the disease, so other factors are of equal or greater importance. . . ." Thus it is difficult to know just what the writer believes on causation, but it is evident that he, long a thoughtful student of the subject and once a firm believer in the theory of infection, is becoming less certain of the rôle of bacteria in arthritis. This state of affairs, confusing and fruitless at the moment, presages advance, because it indicates dissatisfaction with current ideas.

[The eclectic theory does not satisfy the editors of this review. A disease as consistent in its manifestations and course as is atrophic arthritis is assuredly not caused one day by this, the next day by that, factor. Granting the soil and other predisposing, precipitating and aggravating factors all the importance they deserve, there surely must be one prime cause, "X," without which the disease cannot begin or continue. Current confusions, including ideas on polymicrobic origin, are entirely analogous to those held in regard to tuberculosis before the "X" of that disease, the bacillus of tuberculosis, was finally isolated.—Ed.]

Factor of heredity: Buckley[161] stated that heredity is a factor in about 50 per cent of cases and that, probably because of endocrine influences, sympathetic instability, and defective assimilation of calcium, the bodily characteristics of the candidate for arthritis are a slight, spare physique resembling that of persons who are prone to acquire tuberculosis. Walker[174] also stressed the congenital nature of the disease and gave family charts of 13 patients, five of whom had arthritis. He suggested that arthritis is a congenital abiotrophy, resulting from the union of unsuitable types: the union of short and tall persons, of persons with different blood groups, and of persons with straight and with wavy hair.

[Blood groups in 1000 cases studied by Race[139] were what might be expected from a sampling of the general population.—Ed.]

Walker wrote: "These people inherit the diaphyses of all or part of their bones from one racial element and the epiphyses from another. Sometimes this inheritance is one sided. . . . The receptivity of these tissue-masses cannot be expected to be the same to a given hormone. . . ." By some process of reasoning Walker deduced that therefore the pancreas has to work overtime and becomes exhausted. Hence improvement may follow the use of pancreatin and a starch-free diet. In one of Cecil's families the disease was traced through four generations.[165]

[We believe that statements like the above will lead the reader to agree with Cecil that remarks on the hereditary nature of arthritis are usually very loosely presented and unsupported by accurate data. Of course almost every family presents arthritis and many are riddled with senescent arthritis if with no other form. Statistics on heredity and arthritis are erroneous because generally data on the type of arthritis present are not given.—Ed.]

Factor of infection: That some infection, probably streptococcal, is the major factor is still the belief of the majority, and the familiar arguments are presented by many: Buckley,[39, 161] Cecil,[175] Sprunt[176] and Burbank.[149] Cecil, Griffiths,[106] and Dawson, Olmstead and Jost[177] are among those who incriminate hemolytic streptococci. The bacteremic variant of the infectious theory is held by Cecil and by Burbank. The latter has expressed the belief that although the streptococcus is the chief offender, it is not a specific strain but one which has developed the power to ferment mannite and to live in the presence of a comparative deficiency of oxygen. Such organisms possess definite powers of adaptation and mutation, and may reduce their chains to appear as diplococci, or may dissociate into diphtheroid forms, or even may appear as staphylococci similar to Crowe's *Micrococcus deformans*. According to Burbank, the power of adaptation is shown by the fact that the apparent focus of infection rarely contains a streptococcus similar in type or in power to ferment sugar to that isolated from the joints at biopsy. The organism changes its nature from one with invasive properties to one more parasitic in nature, thus avoiding the strong immunologic reactions of the host, which would kill it.

The idea of specific bacterial toxemia apparently has been abandoned in favor of that of bacterial allergy from one or from multiple strains of streptococci or other bacteria. The basis for this idea has been reviewed by Hitchcock[178]: indirect evidence based on cutaneous reactions, variability in cultural results, supposed desensitization by the use of bacterial antigens, and so forth. On the basis of skin tests, Wainwright[179] has tentatively accepted the idea of bacterial allergy. From 94 blood cultures made in 91 cases of atrophic arthritis he recovered streptococci (viridans) in only one case, diphtheroid organisms in four cases and contaminants in seven cases (staphylococci four times; gram-positive bacilli three times). In 14 cases cultures of joint tissues were made: in 12, these cultures were negative; in two, molds were found. The serums in 46 (90 per cent) of 51 cases were found to possess agglutinins for hemolytic streptococci in dilutions varying between 1 to 20 and 1 to 1280. Thus the extent of the dilution was somewhat lower than that reported by others. The presence of such agglutinins in serum of patients who have this disease seems well established, but this does not of necessity indicate a causal relationship. As has been suggested by others, agglutination may be attributable to the presence of natural, not acquired, or specific agglutinins, but the frequency with which it occurs is to Wainwright the best evidence thus far produced that the streptococcus is the cause of the disease.

All of Wainwright's 55 patients who were tested gave positive cutaneous reactions to one or more strains of hemolytic or green-producing streptococci. Whole organisms were used. In 24 cases the reactions were positive to hemolytic streptococci only; in three, to *Streptococcus viridans* only, and in 28 to both types. In 90 per cent maximal reactions were to the hemolytic type, in 10 per cent to viridans; but no single strain predominated in causing maximal reactions. When cutaneous sensitivity exists it does not necessarily also indicate articular or general sensitivity. Objections raised to the interpretation of cutaneous reactions to autogenous vaccines, that they may indicate varying irritability of the patients' skins, natural toxicity of the bacterial species, or perhaps sensitization to certain bacterial groups, must be considered.

Further indirect evidence of a relationship between hemolytic streptococci and atrophic arthritis is, according to Dawson, Olmstead and Jost,[177] provided by a comparative study of precipitins and agglutinins. It was found that there was close approximation, but not absolute agreement, in the capacity of the serums of 71 patients who had atrophic arthritis to agglutinate strains of hemolytic streptococci and to precipitate various group-specific fractions of this organism. These findings suggest that agglutination tests represent a true immunologic reaction, but both agglutinin and precipitin reactions are group-specific and not specific for any particular strain. Whether hemolytic streptococci play a primary or secondary etiologic rôle cannot be concluded.

Discussing the reliability of such indirect evidence, Dawson[180] admitted that cutaneous reactions in his cases have been variable and difficult to interpret. No correlation was found by him between the degree of cutaneous reactivity and the clinical condition of the patient. Cox and Hill[160] found no apparent relationship between variations in the patient's clinical course and his agglutination titers, or between the latter and cutaneous reactions. Cecil's hemolytic streptococcus AB13, however, had greater serologic selectivity for atrophic arthritis than for any other disease-group studied, and the high percentage of serums which contained agglutinins to this strain could not be accounted for on the basis of previous artificial immunization or on that of previous or concomitant streptococcic infections. Cox and Hill concluded that agglutination to this strain has a definite but limited use as a diagnostic aid. Difficulties in interpretation of cutaneous tests were further stressed by Jones and Mote,[181] who noted certain reactions attributable not to the streptococci but to animal proteins injected therewith.

More direct evidence of infection has been sought by others. Blair and Hallman[182] made 57 cultures of synovial fluid and of tissue derived from patients who had atrophic arthritis and 175 cultures from patients who had other types of arthritis. Of the former 75 per cent, of the latter 81 per cent, remained sterile. A variety of organisms was found in the remaining cultures, to none of which etiologic significance was attached. Shapiro[148]

found no organisms in blood cultures of 20 patients who had atrophic arthritis or in blood cultures of 30 patients who had rheumatic fever.

The antihemolysin titer was found by Griffiths[106] to be definitely high in the majority of cases of infective arthritis and spondylitis ankylopoietica (atrophic spondylitis). According to Boys, Gunn and Lang[183] the blood of patients who had active atrophic arthritis (also that of patients who had mixed arthritis, streptococcal septicemia or certain non-streptococcal infections) contained more bacteriolysins to Clawson's strain of *Streptococcus viridans*, than that of normal controls. The blood of patients who were recovering from atrophic arthritis, or who had hypertrophic arthritis, was no more bactericidal than was that of controls.

The conclusion of most of those who uphold the theory of infection is that atrophic arthritis is most likely an infectious disease, although final proof thereof is lacking. Thus, they can sympathize with Key in the recital of his "personal futile attempts to prove the infectious origin of chronic arthritis."[184] From a multitude of cultural studies on blood, synovial membrane and fluid, and on experimental arthritis, he concluded that chronic arthritis of human beings is probably not caused by streptococci, staphylococci or diphtheroid organisms. Nevertheless, atrophic arthritis presents many characteristics which are most satisfactorily explained on the basis of infection of low grade. Unable to discover more direct evidence in support of this theory, workers are now vigorously seeking indirect evidence in the form of skin tests and various immunologic reactions. The value of such evidence is at present impossible to measure, and the current favorite idea that the hemolytic streptococcus is the cause of the disease is built almost entirely on such indirect evidence. The idea of bacterial allergy is attractive because it seems to explain certain cultural and biologic diversities otherwise impossible to harmonize but it should by no means be accepted as an established fact. Vigorous objections to it are being registered, and the value of such evidence as cutaneous sensitivity is sharply contradicted by several investigators. Thus, from their skin tests on 34 patients who had arthritis, using a large number of autogenous strains and controls, Short, Dienes and Bauer[185] found no allergy of the arthritic patient comparable to that in cases of tuberculosis or in certain other chronic infectious diseases. Skin tests, without using several subjects as controls, are without significance. Even so, variations in cutaneous reactions may be explained by differing irritability of the patients' skins, natural toxicity of the bacterial species, or possibly by sensitization to certain bacterial groups.

Wolf[186] listed several objections to the theory of bacterial allergy and concluded: "It seems as though the whole theory of allergy has been introduced as the result of a desire to explain something which it would be far more satisfactory to describe. The conception of allergy does not explain rheumatic arthritic manifestations in general. It does not help us in therapeusis. It really only complicates the problem. The whole theory itself is vague and not clear enough to be used to clear up other problems."

[Bray [187] has tried to describe the so-called allergic joint and has given Pavist's (1933) classification of allergic arthropathy as follows: (1) that of serum origin; (2) that of non-serum origin: (*a*) acute forms simulating acute articular rheumatism; (*b*) allergic hydrarthrosis, either intermittent or chronic; (*c*) chronic rheumatism of allergic origin. Bray added that there is an entire lack of any convincing evidence that the so-called allergic muscular pains in the limbs of children are rheumatic in origin, for among 2000 children attending his asthma clinic, and a similar number attending the rheumatic clinic, there were only two children who gave distinct evidence of both diatheses. With the ideas quoted above from Wolf, Freeman [188] apparently was in complete agreement. All who would connect the terms "allergy" and "hypersensitiveness" with chronic rheumatism and arthritis should read his recent discussion thereon. According to him, the use of dermal reactions in rheumatism affords little or no assistance in settling the question of allergy. In the first place, the reactions are practically never similar to those seen in true allergic diseases. He concluded that a "fog of research" blankets the whole subject of allergy in rheumatism. "We are working in a fog and have as yet no clear vision. The word allergy is, to my mind, not a gleam of sunshine breaking through, but an extra wisp of fog."—Ed.]

Factor of circulatory disturbance: In many cases there are obvious alterations in the general blood flow: low blood pressure; cold, clammy extremities, and lowered cutaneous temperature. Some investigators, chiefly Pemberton, have laid considerable stress on such alterations as probably being of major etiologic importance. The exact nature and reason for them has not been fully determined. Kovacs [189, 190] Wright [191] and Hench [192] have agreed that they do not represent derangements of large vessels. Many workers consider them attributable to capillary vasoconstriction. Thus, Kovacs found small, constricted capillaries in 53 per cent of cases, a slow blood flow in 65 per cent, and a decreased number of capillaries in nail beds peripheral to swollen joints in cases of atrophic arthritis. Hench was unable to find consistent alterations: some patients exhibit vasomotor alterations long before, others not until long after, the onset of arthritis, and still others not at all. Capillaries are more often dilated with a sluggish flow than constricted. After sympathectomy, with improved arterial and arteriolar circulation, capillaries of arthritic patients are not more, but less, dilated; however, the flow within them is faster. Since such circulatory alterations are so inconsistently present they must represent, according to Hench, not the cause of the disease, not even an essential part of the disease, but "a complication appearing at varying times and in varying degrees as the sympathetic nervous system is perhaps variously affected by the toxins of the disease." Wright, Kovacs and Hench agreed that capillary alterations are probably not an etiologic, but may be a definite aggravating factor, worthy of correction.

Arteriosclerotic changes were roentgenographically evident in the examination of 38 per cent of 90 patients studied by Nissen and Spencer.[193] Many were less than 40 years of age and of these, 27 per cent were so affected. No definite relationship was found between the sclerosis on the one hand and the hypertension or the cardiorenal abnormalities on the other.

Of 72 cases of hypertrophic arthritis, in 78 per cent arteriosclerosis was present: 7 per cent of the patients were below the age of 40 years. The writers could not conclude whether these findings were coincidental, or of etiologic significance.

[No figures are given on the incidence of sclerosis in non-articular disease affecting patients of similar age groups, and no correlation is established between the anatomic situation of the sclerosis and that of the arthritis.—Ed.]

Factor of altered metabolism: Different things are meant by different people when they use the term "altered metabolism." Varied is the evidence pointed out as indicating the presence of altered metabolism, and the representations made in favor of the theory of disturbed metabolism are no more, indeed less, definite than those in behalf of the theory of infection. Fletcher is of the belief that the value of Pemberton's low-calorie, low-carbohydrate diet lies not so much in the curtailment of the latter as in the fact that such a diet is high in vitamins, especially vitamin B, and that vitamins act more effectively when ingested with a ration low in carbohydrate. With this idea, Pemberton, Peirce and Bach[194] expressed disagreement. Patients who received a low-carbohydrate, very low-vitamin diet improved as well as those who received a low-carbohydrate, high-vitamin diet.

Patients who have atrophic or hypertrophic arthritis do not tend to follow a diet essentially different from the normal in total calories or in relative amounts of proteins, fats and carbohydrates, according to Sladen, Ensign and McColl.[195] However, on close analysis many reveal a hidden dietary error—a tendency to choose carbohydrate foods of small bulk and containing small amounts of minerals and vitamins. Correction in the kind, not in the amount, of carbohydrates is in order.

The well known ideas of Pemberton and his colleagues on the metabolic and nutritional aspects of the disease have been carefully reviewed again.[166, 196] Apparent alterations in sugar tolerance and in metabolic rates do not necessarily indicate pancreatic or thyroid deficiency but are probably dependent on the curtailment of blood flow to various tissues, especially to muscles. The sugar tolerance was found by Nissen and Spencer[197] to be normal in 43 per cent and abnormal in 57 per cent of a group of 222 cases of arthritis, represented by patients, 82 of whom had atrophic arthritis, 62, hypertrophic arthritis, and the remainder, arthritis of other types. Correlation was not found between the sugar tolerance on the one hand, and, on the other the age or sex of the patient, the duration or activity of the arthritis, or the presence of foci of infection, of hypertension or of arteriosclerosis. An abnormal tolerance did not necessarily become normal when the disease became inactive. Nissen and Spencer queried whether the etiology of arthritis might lie in disturbed function of the pancreas, liver, suprarenal gland or pituitary body, such that the autonomic control of the body is affected without a diabetic syndrome being present.

An undefined type of food deficiency was suspected as the cause of the disease by Wright,[150] who particularly prescribed whole wheat flour instead of white flour, and by Burnett and Ober.[154] According to the latter, the deficiency does not occur from lack of a complete diet but from incomplete digestion and absorption of food, leading to failure of nutrient substances to construct or preserve normal bone and cartilage. Contrary to the belief of most investigators, that arthritic patients tend to exhibit definite delays in passage of a meal, Burnett and Ober expressed the belief that such a patient tends to hurry along a meal, an index of incomplete digestion and absorption. The majority of patients eat too much fat or fruit and not enough vegetables. Rather than favoring more roughage or a more rapid emptying time of the bowel the authors named favored slowing down the passage of intestinal content to a normal rate to permit anabolic nutrition.

[This entire discussion is highly theoretical. No proof is offered for statements made.—Ed.]

Snyder, Traeger, Fineman and Zoll[198] adopted the opposite and more common view that intestinal, particularly colonic, stasis is present, and that this is exhibited by roentgenograms of redundant, atonic, dilated colons and by certain symptoms of dyspepsia. With this view Hartsock[199] expressed agreement.

[Objections to this viewpoint are contained in last year's review.—Ed.]

The idea of the overproduction by the arthritic patient of an acid-ash from foods rich in proteins and carbohydrates has been advanced again,[200] but Boyd[201] investigating the chemistry of urine and sweat of rheumatic patients could not conclude that the beneficial effects of heat were attributable to the elimination of acid constituents. The induced sweat of arthritic patients was chemically the same as that of normal persons.

A revival of sulphur therapy is being attempted as the result of Cawadias' theory (1927) that the cells of an arthritic patient have lost the ability to retain sulphur. Sullivan and Hess,[202] and Sullivan[203] expressed the belief that the cystine content of the finger nails of arthritic patients of the "infective" or "mixed types" is definitely low, an indication of disturbed metabolism of sulphur. The cystine content of the nails of 103 arthritic patients averaged 9.8 per cent (7.2 to 13.1 per cent) as compared to an average of 11.7 per cent (10.2 to 13 per cent) in the nails of 30 normal persons. According to Sullivan and Hess, the body uses compounds of sulphur, cystine, cysteine and glutathione to render injurious material innocuous, a detoxication process. The low cystine content of nails may imply a factor of abnormal intoxication depleting their content of sulphur. Among 25 patients who had atrophic arthritis, Woldenberg[204] found even lower values for cystine in nails (6.5 to 9.8 per cent; normal values presumably 12 to 12.5 per cent). However, by Senturia[205] no variations from the normal glutathione content of blood (30 to 40 mg. per 100 c.c.) were

found in the blood of 18 patients who had atrophic arthritis, nor in the blood of 27 patients who had hypertrophic arthritis, nor in that of eight who had periarthritis.

Factor of endocrine relationships: A commonly seen but infrequently discussed phenomenon of the arthritic patient was considered by Rugh [206]: the exacerbation of arthritis in the course of menstruation. Recalling the work of Macht, Rugh suggested that the menotoxin may be responsible. Aside from the conjectures of Nissen and Spencer,[197] and of Walker,[174] noted in the foregoing, and the statements by Pemberton and Bach [166] and by Ober [153] that lowered metabolic rates are frequently seen, no other data on endocrine abnormalities were forthcoming.

Conclusions on etiology and pathogenesis: From this mass of confusing, sometimes conflicting, data one cannot as yet form any conclusive ideas on the etiology and pathogenesis of the disease. It is obvious that no evidence has been brought forth to change the statement of the American Committee for the Control of Rheumatism, that to date no one etiologic factor, no single infection, dietary abnormality or metabolic derangement has been conclusively shown to be the prime cause of the disease.

Treatment. General remarks: The need for a broad approach to the problem of treatment is obvious from the foregoing and was stressed by Irons,[207, 208] Cecil,[165, 175, 209] Pemberton and Bach,[166] Haden,[145] Archer,[146] Holbrook and Hill [210] and Holbrook.[159] One must initiate a therapeutic program with an open mind, without prejudice against the theories of others, because any program of treatment based on one theory or on one causative factor will fail in clinical use. A physician must not concentrate on only one form of treatment or he will become a faddist. In selecting his physician a patient probably will do best by choosing a well-rounded internist. There is no one specific, no one standard form of treatment. Individualized, not routine, treatment of each patient is required, and the patient, not just the disease, must be vigorously studied and cared for. Because of the obvious importance of interrelated factors, correction of whatever abnormalities the patient presents is necessary.

[One gladly accepts the choice of a well-rounded internist if he be really interested in the disease. Too often "the well-rounded internist" is conspicuous for his lack of interest in arthritis and by his failure to familiarize himself with the nature of the disease and its victim. Many indulge in half-baked ideas and one-sided methods of treatment, accepting too readily the dicta of faddists. It seems obvious that, in spite of the absence of any specific treatment, best results will be obtained by him who has a broad experience with the disease and who, whether he calls himself a general practitioner, an internist, or even a "rheumatism specialist," has vital interest in the disease. To some extent official medicine in this country has been inclined to oppose the development of arthritic clinics and special institutions for the care of arthritic patients. European governments are frankly partial to such institutions. Certainly therefrom should accrue to the army of arthritic sufferers benefits similar to those which have been derived in the field of tuberculosis and heart disease.—Ed.]

At first glance it would seem that treatment of the disease varies markedly in different clinics: in one place removal of foci seems to be stressed; in another, postural care; in still another, dietary measures; in others, climatic care, sulphur or gold therapy, sympathectomy, and so on. As a matter of fact most physicians treat patients in much the same way although their writings may be calculated to emphasize some particular idea on treatment or cause. Cecil questioned 15 colleagues in various parts of the country as to their favorite therapy. Replies indicated that rest, removal of foci, physiotherapy and climate were favored; foreign protein, transfusions of blood, drugs and intestinal hygiene, and fever therapy ranked low in their estimate. A diet low in carbohydrate and a streptococcal vaccine won moderate recognition. Controlled experiments with various types of therapy were performed by Holbrook and Hill. Of 100 patients, each was subjected to one of the following: removal of foci, transfusions, administration of vaccine, or heliotherapy, and each was observed for from months to years. Results emphasized the non-specificity of any one measure. In consequence, a coördinated program of those measures found by experience to be most useful is essential. It is suggested that many measures obviously of slight or of questionable value should be discarded and the patient and his physician concentrate their energies and finances on measures of proved worth.

Foci of infection and their removal: Infection in foci may not precede nor be the cause of the disease but may rather be the result of the disease. As a result of basic, general, nutritional and metabolic derangements, producing localized alterations in nutrition, they may appear more frequently after the disease has started. Ducker [211] expressed approval of this viewpoint, put forward by Pemberton, and has noted the tendency for successive foci to develop after the original focus has been removed. Thus, a tooth may become infected as the result of disturbed nutrition incident to arthritis.

Foci of infection were found equally present (17 per cent) in cases of both types of arthritis (3004 of atrophic arthritis; 1335 of hypertrophic arthritis) studied by Steindler.[212] Of those cases of atrophic arthritis and of hypertrophic arthritis in which focal infection was present, the tonsils were infected in 55 per cent and 64 per cent respectively, teeth in 17 per cent and 23 per cent, sinuses in 46 per cent and 57 per cent, the biliary tract in 1.5 per cent and 7 per cent, and the genito-urinary tract in 6 per cent and 5 per cent. Striking immediate improvement from removal of foci was noted in 35 per cent of cases of atrophic arthritis and in 20 per cent of cases of hypertrophic arthritis. Lasting benefits were obtained, however, in only 15 per cent of cases of atrophic arthritis and in 8 per cent of cases of hypertrophic arthritis. To Key [213] it seemed strange that Steindler found foci of infection in only 17 per cent of cases of both types. It has been said that almost no one reaches adult life with normal tonsils and teeth. The effect of removal of foci in these cases was not impressive—many more

than 35 per cent of patients are benefited by other measures or get well without therapy.

It is erroneous to believe that tonsillectomy can adequately remove a focus of infection. Infection is not localized in the tonsils but is spread widely over adjacent nasopharyngeal tissue which may appear normal, according to Solis-Cohen.[214] From 95 per cent of normal appearing nasopharynges he got positive cultures for infecting organisms, often the same organisms as those found in removed tonsils. The terms "removal," "eradication" or "elimination" of foci of infection are only relative; and to counteract the toxins elaborated by the irremovable infections, stimulation of antibodies and of bactericidins is necessary. This is done, as previously outlined, by Solis-Cohen's method of vaccine therapy based on pathogen-selection (the use in his vaccine only of organisms which grow in, and are not killed by, the patient's own serum). The dangers of silent sinusitis have been discussed again by Snyder, Fineman and Traeger,[215] the fourth time a report on this same series of cases has been published.

Early eradication of foci has been to Cecil,[175, 209] and to many others, the keystone of the arch of treatment. To Cecil removal of infected tonsils is the most important, the care of infected sinuses and teeth next in value. Even tonsils which arouse suspicion should be removed early. Devitalized teeth are removed only when periapical infection is visible, and in the treatment of sinusitis Cecil wrote that he followed the advice of a "none too radical laryngologist." With this plan, Archer,[146] Pemberton and Bach,[166] Climie,[5] and Sprunt [176] expressed agreement. Foci of infection should be removed early, the sooner the better, and one should not "wait till the patient is stronger." Removal of a focus after it has spent its force cannot repair a joint and not only is of no value but may be dangerous. But foci must be removed "intelligently" [207] and "at the proper time." [145] Holbrook [159] expressed the belief that early removal of foci is of much greater value in febrile cases (infectious or "b" group), with a subacute onset, than in cases of the more chronic and insidious type. Removal of foci in the latter group may be disastrous unless proper precautions (a building-up process; measures against fatigue, exhaustion, constipation and malnutrition; preliminary transfusion) are taken. To R. and J. Kovacs [140] results of removal of foci have been disappointing.

Vaccines: From published reports it is very difficult, if not impossible, to determine the value of vaccines. They are prepared and given in so many different ways, almost always in conjunction with other therapy, and rarely are results with a control series given. Statements relative to vaccines must be considered as statements of impressions, not as declarations of indisputable facts, even though, often, they are made after long experience. The situation is difficult if not impossible to remedy, for few physicians or patients have sufficient faith to rely on vaccines only, and the natural course of the disease is varied by seasonal and other remissions. The majority of investigators now believe that they are attempting desensiti-

zation, not immunization, and therefore favor very small doses, which do not produce significant reactions. Systemic reactions are to be avoided. Minor local and focal reactions may be permissible if followed by a significant period of euphoria (improvement reaction). Some workers even avoid all focal reactions and seek to use the smallest dose which gives relief without reaction.[216]

When vaccines are given, they should be administered for long periods: "several months at least," [209] "for 6 to 12 months," [217] "for 6 months to 2 years." [218] Results should not be evaluated until after three or four years,[148] to determine whether a temporary or a lasting effect is obtained. Cecil [165, 175, 209] expressed himself as favoring administration of his stock, hemolytic streptococcal vaccine intravenously or subcutaneously; in many cases he has obtained gratifying results. Of 35 patients treated by Marvin [219] with Cecil's vaccine, five were markedly benefited, nine moderately improved, 10 slightly improved, and 11 not improved. Discouraged by previous subcutaneous or intramuscular administration, he gave the vaccine intravenously. No control series was reported. With Cecil's vaccine given intravenously, Higgins' [30] results have been far from satisfactory but there was an occasional brilliant result.

Crowe's polyvalent vaccine (staphylococci, streptococci) was favored by Carlson,[220] Nutter and Watson,[221] and Nutter,[222] Wright,[150] and Adamson.[6] Of 137 patients who had chronic (undifferentiated) arthritis, treated by Nutter, 65 became symptom-free and remained so for at least five months.

[No other statistical results were given.—Ed.]

Bacterial filtrates, such as are used by Small, were favored by Cohen [223] and by Lawler.[114] The pathogen-selective method of preparing autogenous vaccines was favored by Solis-Cohen,[214] and by Murphy,[217] who used vaccines in addition to other measures. Cutter's diluted cold vaccine (staphylococci, streptococci, pneumococci, *Micrococcus catarrhalis,* Friedlander's bacillus, and influenzal bacillus) was used with good results by Sherwood [141] in 220 cases of chronic arthritis of various types. "Usually after 12 to 20 treatments the patient will be much relieved."

[Presumably no other treatment was given, but no controls were studied.—Ed.]

Of 28 patients treated by Wainwright [179] with vaccines prepared from strains of microörganisms to which patients were skin-sensitive, 75 per cent were benefited: five of eight bed-ridden patients were able to be about. Subsequent skin tests gave evidence of less sensitivity or became negative, the patients' agglutinins increased and sedimentation rates diminished. Similar vaccines were used by Rogers [224] in 15 cases: in mild cases improvement was marked; in more severe cases less improvement was noted. Anaerobic, as well as aerobic organisms must be included to obtain results. Although one would prefer to use strains presumably responsible for the patient's sensitization, the determination of such strains was, to Hitch-

cock,[178] a formidable matter; consequently stock strains of hemolytic streptococci were used.

The methods used in preparation of these various vaccines are to a large extent based on false premises and on assumptions that are not susceptible of proof, according to Short, Dienes and Bauer,[185] who pointed out the inadequacies of skin tests, complement fixation tests, and the pathogen-selective method. Skin tests do not provide a sound method for determining a patient's susceptibility to autogenous organisms. None of the different methods recommended for the selection of strains from which to make specific vaccines has a solid theoretical or experimental foundation. Such results as are obtained are those of the non-specific effect of the vaccines. Buckley [39, 161] agreed that "specific vaccines" are probably neither specific nor essential. In his hands, Pondorff's cutivaccine has given variable but interesting results. Vaccines have a definite but distinctly limited place in the scheme of therapy according to Holbrook,[159] Irons,[207] and Pemberton and Bach.[166] Used alone, they rarely cure patients. Various preparations were administered variously by Holbrook [159] and Holbrook and Hill [210]; only occasionally was improvement noted that was not easily accounted for otherwise. Minute doses of vaccine administered intravenously gave the most favorable results. More cripples than cures may result from indiscriminate and injudicious use of vaccines.[39, 159] Unsatisfactory results with Cecil's and with Clawson and Wetherby's vaccine were obtained by Archer [146] who expressed the belief that such results as are obtained may be largely psychogenic. No striking results were noted by Shapiro.[148] In the study by Cox and Hill,[160] vaccine therapy was not followed by correlated changes in agglutinins.

Regarding the intestines as a focus of infection, and considering the value of "intestinal vaccines," Buckley [161] expressed the opinion that the possibility of the infecting organism becoming an inhabitant of the bowel can be ignored. "There is sufficient evidence that bacteria do not normally enter the circulation from this source; and the toxins, if absorbed, are probably greatly modified if not destroyed by passing through the lines of defence."

Foreign proteins: These substances seem useful to some investigators.[176, 225] Brooks [142] continued to favor the use of his hemoprotein, given without reactions, in conjunction with other measures. Lawler [114] used typhoid bacilli as the most available means of producing fever in 36 cases of arthritis of various types. Improvement was generally only temporary. Wetherby [147] considered typhoid vaccine of little value.

Diet: Attention to the ideas concerning the factor of nutrition and metabolic derangements will explain the supposed rationale of the various popular "rheumatism diets." The same familiar diets or slight modifications thereof are again candidates for approval: the low-carbohydrate, low-calorie diet; the high-vitamin, low-carbohydrate diet [222]; the high-calorie, high-vitamin diet [140, 210]; the individualized diet. To his familiar arguments

in favor of a low-calorie, low-carbohydrate diet Pemberton and his colleagues,[166, 194] added another; namely, that such a diet exerts a definite dehydrating effect on body tissues in both types of arthritis.[196] The loss is in pathologic, not in physiologic fluid. Definite reduction in periarticular swelling and articular pain are realized.

[This interesting suggestion needs further confirmation. The water balance studies in these experiments were approximate, not absolutely controlled.—Ed.]

Various modifications of the diet just mentioned were favored: Avoidance of free sugar by Douthwaite,[121] a starch-free diet and administration of pancreatin by Walker.[174]

[Has pancreatin ever been shown to have any provable physiologic effect? We do not believe so.—Ed.]

Pemberton's diet seemed of little benefit to Wetherby's patients.[147] Other investigators still restricted purine foods "because the blood uric acid is often high."[226]

[We disagree with this; the blood uric acid is rarely high and restrictions of protein generally are not indicated.—Ed.]

As previously noted a hidden dietary error was corrected by Sladen, Ensign and McColl[195] by rearranging the kinds, not the amounts, of carbohydrates ingested.

The majority of investigators expressed the belief that no one diet is of value. Constipation, inanition and obesity are all to be avoided or corrected by a diet arranged for the individual patient. The details of their diet for anabolic nutrition were outlined by Burnett and Ober.[154]

Additional intestinal therapy: Colonic irrigations were recommended by some,[222] avoided by others.[175, 210] They may be fatiguing if given too often and should rarely be given to people who are on "a low nutritional equilibrium."[166] To control intestinal elimination, mineral oil, agar-agar, oil retention enemas, glycerine suppositories, and abdominal exercises were recommended by some,[210] but were frowned on by Burnett and Ober.[154]

Blood transfusions: Transfusions of 250 to 500 c.c. of blood may be indicated in cases in which there is severe anemia.[140, 166] They may be helpful in subacute and early, chronic, febrile cases but are of little value in the very chronic, afebrile cases in which pathologic changes are advanced.[159, 210]

Medicines: Many medicinal preparations are used generally as adjuncts to more important measures: iron, arsenic, liver extract, various analgesic substances, cod liver oil, viosterol, haliver oil, potassium iodide, thyroid extract, wheat germ, yeast, nitrites for vasodilation in selected cases, strychnine or nux vomica for fatigue. Cecil[175] agreed with Haden that neoarsphenamine gives good results occasionally, but Moltke[163] saw no rationale therefor. Wheeldon[227] wrote that he used calcium ortho-iodoxybenzoate "to improve peripheral circulation."

Preparations of gold: Various preparations of gold (solganol, allo-

chrysin, myocrisin) are being used in continental Europe. Further experience with allochrysin (sodium aurothio-propanol sulphonate) were reported by Forestier,[228] who in five years has treated therewith 500 cases of atrophic arthritis; 70 to 80 per cent responded well. In 50 per cent of early cases, and in from 20 to 30 per cent of those in which the arthritis was of more than two years' duration, permanent cure was reported after two to five series of injections. "Myocrisin" is injected weekly; the individual dose is 0.1 to 0.2 gm. and the total dose 1.5 to 2.0 gm. in one series. Untoward reactions may be noted in the skin and in the respiratory, alimentary, nervous, and urinary systems. Nephritis has been produced in man and in animals; the gold is excreted mainly through the kidneys. Jaundice, leukopenia, or febrile reactions may be observed. Slot and Deville[115] treated 14 patients with solganol and improvement was "great." Buckley used allochrysin "in a certain number of cases with some promising results." The sulphur therein may act synergically with the gold.[161] Cecil's[175] results with salts of gold were "not striking."

Compounds of sulphur: A renaissance of sulphur therapy is current. Weekly or biweekly injections of sulphur are generally given intramuscularly: 20 mg. in oil or 5 mg. intravenously. After 10 or 12 doses have been given, a rest of 10 days is permitted. Two or three courses are generally prescribed. Untoward reactions, aside from occasional, small, cutaneous sloughs or febrile reactions, were not reported, and presumably there are no contraindications. Senturia[229] used sulphur-diasporal in the treatment of 55 patients who had atrophic and hypertrophic arthritis and gave it also to five patients who had fibrositis. Of this total, 75 per cent were "improved"; 31 per cent markedly so. From 10 to 76 injections were given. Four of seven patients treated by Sullivan and Hess[202] were "appreciably" or "markedly" improved. Later all of six patients were improved.[203]

[The same patients?—Ed.]

Sullivan[203] noted definite increases in the cystine content of the nails during therapy. Of 100 patients treated by Woldenberg[204] the majority became free of pain after five or six injections. However, all received a variety of other forms of treatment. In seven cases, Argy[230] noted no improvement until after five injections; thereafter, in six improvement was noted. It is suggested that better results are to be expected if the cystine content of the nails is low before treatment. To Cecil,[175] however, injections of sulphur have been disappointing.

[In none of these series, practically all of but a few cases, have control studies been carried out. In the one fairly large series many other forms of treatment were used in addition to sulphur. It seems well to wait for controlled studies before considering that treatment with sulphur deserves to be resurrected from limbo simply because "new" colloidal preparations are available. Our brief note in last year's review, that such therapy was being revived, has already been used in advertising matter praising treatment with sulphur, although not the faintest approval was voiced by us.—Ed.]

Histamine and choline: The recent use of histamine for rheumatic diseases was initiated by Deutsch (1931). The claims for such treatment in Germany seem extravagant. From European literature Kling[231] collected data on 554 cases of arthritis, neuritis or myalgia so treated by various physicians. Of 316 patients who had myalgia (myositis), 96 per cent were "improved or cured." Of 85 patients who had arthritis, more than 90 per cent were improved. Histamine, given by cataphoresis, ionization, in ointments during massage, or by the scratch method presumably produces capillary and arteriolar dilatation, correcting an altered peripheral circulation. Kling's results[231, 232] were less striking. Of 32 cases of myositis, in 75 per cent he had a favorable result. Of 14 patients who had hypertrophic arthritis, eight were helped. No conclusions were reached as to results in 24 other cases of arthritis. The use of histamine, by inunction or ionization, was praised by Mackenna,[233] for fibrositis and chronic villous arthritis. It does not change the course of the latter but relieves symptoms for variable periods. With its use, it is "possible completely to cure fibrositis and neuritis." Histamine and thiohistamine are particularly useful in the treatment of periarticular arthritis accompanied by cold, cyanotic fingers, according to Shanson and Eastwood[116] who favored intramuscular injections rather than ionization. The benefits of foreign protein therapy, according to Buckley,[39] may be attributable to liberation thereby of a histamine-like substance.

[It is to be noted that here again the number of patients treated was generally small; no real control studies were instituted; a confused nomenclature was used; data on the type, severity and duration of the arthritis were almost wholly lacking, and certain of the conditions cured (for example myalgia) were of limited duration.—Ed.]

In a series of papers, R. and J. Kovacs[140, 234] and J. Kovacs[189, 190] gave the basis for preferring ionization with mecholin (acetyl-beta-methylcholine chloride) rather than oral, subcutaneous, or intravenous use of histamine, acetylcholine or nitrites. The general and local (vasodilating) effects of these were compared. The Kovacs contended that the action of mecholin is more lasting, less unpleasant, and more effective. Of 30 patients who had atrophic arthritis, 90 per cent were improved. Patients who had osteoarthritis were also improved but not more than with more established methods.

Climatotherapy: Climate provides no panacea.[166] However, a stay in a high, dry climate may be advantageous in some cases[209] but not without the use of other forms of therapy.[159, 210] In and about Tucson, Arizona very few native white people have arthritis. The incidence of the disease among local Indians is less than among those elsewhere. Many patients, unrelieved at home, obtain notable relief in Arizona "but it must be understood that without the proper routine of living (a coördinated program of therapy), arthritis even on the Tucson desert can continue as a sad and crippling disease."

Rest and movement: The great value of adequate rest for the inflamed joints, and also for the fatigued body, of the arthritic patient was stressed by many. "If one single remedial agent was to be chosen, rest would be the one selected."[151] "As in tuberculosis, so in arthritis, rest is the keystone of the arch."[166] "Motto—no weight bearing on swollen joints."[235] "Rest till signs of inflammation have subsided."[236] As the acute blends into the subacute and chronic stage, rest may be sharply overdone. The recumbent patient who has arthritis must not be taught only how to lie correctly but must exercise in bed as the daily condition of the joints permits. "A movement a day keeps adhesions away."[235] Early motion is necessary and often too much rest is prescribed. When, because of pain and stiffness, the patient does not coöperate in the prevention of deformity, the way is paved for the production of arthritic derelicts. "The price of comfort is crippling."[5] Hench and Meyerding[237] have presented examples of these arthritic derelicts—patients who have allowed themselves, or who have been permitted, to become human pretzels from grievous deformities generally induced by rest, often deliberately prescribed. A detailed and diagrammatic synopsis of methods of prevention of deformity available for use by physicians in the patient's home was given by Hench and Meyerding. Swaim[238] has outlined again the tenets of the Boston school concerning postural and other exercises, and measures for the prevention of deformities.

Physical therapy and manipulation: As usual, each form of physical therapy has its advocates. The value and indications thereof are too well-known to need review here, but the merits of many are cited: various forms of heat,[239, 240] paraffin baths,[241] infra-red and diathermy,[242] effervescing immersion baths,[243] contrast baths,[244] fangotherapy,[245] hydrotherapy,[246, 247] applications of cold,[248] manipulation.[249, 250, 251, 252, 253, 254] The teaching of physical therapy to undergraduates and to the general practitioner who needs to know much more about it was discussed by Cutter and Coulter[255] and by Kovacs.[256] A central registry can inform any physician of the nearest physiotherapists.[257]

Fever therapy; artificial hyperpyrexia: This is the newest form of physical therapy. Experience with it in treatment of atrophic arthritis has shown that results therein are not nearly as good as they are in gonorrheal arthritis. The first dozen reports were analyzed in last year's review. Using diathermy-hyperpyrexia (five hours at an oral temperature of 104.4° F.; one to five sessions) in the treatment of 12 patients, Nicholls, Hansson and Stainsby[258] noted cures or marked relief of none, moderate relief of 25 per cent and little or no relief of 75 per cent. They considered it a trying ordeal for the patient and did not feel justified in continuing its use. Osborne and Markson's third and fourth reports[27, 359] concerned results of 188 treatments administered to 28 patients. The usual course was eight treatments (each of 6 to 8 hours at an oral temperature of more than 104° F.). Remissions were induced in many cases, and from 50 to 70 per cent of the patients, grouped according to severity of the disease, were

considered improved. Merriman, Holmquest and Osborne [260] recently have advocated the use of an inductotherm to decrease expense and for the sake of ease in therapy. About 75 per cent of 40 patients treated by Simpson [22] with radiothermy or in heated cabinets (Kettering hypertherm) were definitely improved. Diathermy-hyperpyrexia was advocated by Jones.[23] A safe method of producing fever, by hot baths in the patient's home, was outlined by Currence.[261] Cecil [175] preferred injections of typhoid vaccine to fever induced by diathermy. For discussions on the relative merits of various methods for producing fever, and for details on the physiologic reactions produced thereby, various new references are available.[26, 262 to 272] Hoverson [270] has reported the case of a paretic patient who survived an uncontrollable hyperpyrexia that rose to 110.5° F. Short and Bauer,[271] and Hench, Slocumb and Popp [272] recently have reported their results. In general the effect of fever therapy in atrophic arthritis was disappointing. Satisfactory remissions were occasionally induced. About 25 per cent of patients noted definite improvement. None were cured. Hench [273] also has summarized the entire national experience with fever therapy for atrophic arthritis: of about 200 patients so treated less than 10 per cent became symptom-free; about 25 to 30 per cent noted some relief. Results with various methods do not differ materially. The choice of method resolves itself into the selection of that which is safest, least expensive and most comfortable for the patient. Hench expressed his preference for humidified, heated cabinets. Untoward reactions are rare when the procedure is supervised, in a hospital, by trained nurse-technicians and an attending physician. Severe reactions, even death, are occasionally encountered. The Council on Physical Therapy of the American Medical Association recently [28] reported on the results obtained by 4809 patients, who had different diseases, treated by various physicians, with different forms of fever therapy. Twenty-nine deaths were noted, many of them among neurosyphilitic patients.

[With care in selection of patients, and with skilled management, the procedure is essentially safe.—Ed.]

Surgical Procedures. Synovectomy: Occasionally synovectomy is indicated for an old, boggy, proliferative, inflammatory process in a knee that is unresponsive to conservative therapy, and if the condition is not accompanied by much arthritic activity in other joints.[274] Busby [275] expressed the belief that synovectomy is at times necessary to correct an otherwise uncorrectable articular focus of streptococci.

Sympathectomy: This procedure was initiated in selected cases of arthritis by Rowntree and Adson (1927) and its physiologic rationale was further outlined by Hench and Craig (1931). It is a method of value in certain cases.[276] In Young's [277] experience "several cases of distressing and seriously disabling chronic polyarthritis of the hip, knee, and ankle have been relieved almost beyond belief by lumbar sympathectomy." In treat-

ment of a child who had early swelling and deformity of the legs, resection of lumbar trunks by Robertson [278] "caused or immediately preceded a rapid and complete return to normal." In another "more advanced and severe case," after operation, "pain and the vascular condition of the lower limbs were very markedly improved. The patient's comfort was greater but that was the net result." Robertson felt that these "results were striking and would encourage one to operate in these cases at as early a stage as they can be found." Unilateral cervicothoracic sympathectomy was performed by Hosford [279] on an elderly woman who had marked arthritis of the joints of the right arm. "Complete pain relief and a considerable increase in the use of the hand and arm" were the results.

[Some question the rationale of sympathectomy in a disease presumably infectious. Those who initiated and advanced the trial use of this procedure for atrophic arthritis were not proposing a "specific measure" for a disease of supposed neurogenic origin. They were advocating a measure designed to counteract a "complication" variably present in differing degrees in a disease which might well be infectious. The complication—a vasomotor disturbance presumably responsible for an inadequate blood supply to affected and already seriously embarrassed extremities—may occasionally be of sufficient severity to warrant attempts for its correction in the most complete and lasting way possible—sympathectomy. Sympathectomy is therefore regarded by its proponents as a sort of continuous infusion of the patient's own blood in behalf of just one part of his body—the peripheral portions of his cold clammy arthritic extremities. If thereby the blood flow thereto is significantly augmented (as indirect, not direct, evidence seems to suggest) and if the patient's blood is still sufficiently potent in its concentration of specific and "non-specific" healing substances, good results may be obtained, analogous to repeated transfusions. If such be not the case the infusion via sympathectomy will be of no more value than an ordinary transfusion to a hopelessly sick or dying man. The crux of the matter lies in proper selection of the patient.

Since the original workers in this field are wisely postponing their final report and because others have performed sympathectomy on but three or four cases, the value of sympathectomy in atrophic arthritis is not yet established.—Ed.]

The selection of cases for sympathectomy was again discussed by Brown, Craig and Adson.[280] Suitable are young patients who have fairly early atrophic arthritis, especially in hands and feet; who have cold, clammy extremities and little bony change, and who are unrelieved by conservative measures. A higher grade of postoperative vasodilation is obtained in the hands and feet than in less peripheral tissues. Several questions are frequently asked: What changes are present in excised tissues? Does the operation produce significant vasodilation? Are the postoperative changes permanent? Do ill effects eventually accrue to body tissues? Is there a possibility that sympathectomy might eventually produce neuropathic joint disease? [274] Changes in the excised ganglia, according to Craig and Kernohan (1933), were comparable to those found in ganglia removed at necropsy from patients unaffected by arthritis or derangements of the sympathetic nervous system. Kuntz [281] found the same changes in ganglia removed from 19 patients who had chronic polyarthritis, but he was inclined to

emphasize their departure from normal and he disagreed with Craig and Kernohan chiefly as to the appearance of normal human ganglia.

[Since what is the normal appearance of a ganglion of man has not been established, differences of opinion will arise. Kuntz assumed that ganglia of normal human beings and of normal animals are identical but since this has not been established, it, like previous ideas, constitutes only an opinion. One might disagree with him when he assumes that the free, intracapsular elements around ganglion cells are phagocytes rather than satellite cells of the ganglion cells. At any rate, the changes observed in the ganglia in individual cases were not specific and could not be related directly to arthritis or to other diseases in question.—Ed.]

Although they were unable, by the injection of an opaque substance, to visualize dilatation of smaller vessels after unilateral sympathectomy of dogs (such as was demonstrated by Horton and Craig, 1930) McMaster and Roome [282] found an increased cutaneous temperature most marked distally on the side on which operation had been performed. They, therefore, assumed that such vasodilation as occurs probably takes place in smaller arterioles and capillaries.

[McMaster and Roome used a thick suspension of vermillion water color. Horton and Craig used metallic mercury, a heavier substance of greater penetrability.—Ed.]

Studying vasomotor reactions of cats on which sympathectomy had been performed, Rosenblueth and Cannon [283] suggested the presence of vasodilator centers and central tracts susceptible of direct stimulation. In sympathectomized animals, dilator fibers in dorsal roots are probably efferent paths of response to stimulation of the depressor points, and also to stimulation of the vasomotor reflexes and of the dilator impulses responsible for various reactions such as a fall in blood pressure attending struggle. Granting that certain permanent alterations are produced by sympathectomy in man, are they eventually harmful to various organs? In animals 22 to 42 months after operation, Clark [284] found no gross changes which could be attributed to absence of the sympathetic system. Thymus glands were infiltrated with adipose tissue. There was no gross evidence of regeneration of sympathetic trunks or ganglia, and histologic studies disclosed practically no changes except for minor ones in the thyroid glands or testes. These, and the studies of Brown, Craig and Adson, would lead to the conclusion that in man permanent vasodilation, but no harmful effects, are produced by sympathectomy.

Splenectomy in arthritis with splenomegaly: Following the example set by the admirers of Still, from time to time various names have been attached to the combination of arthritis in association with alterations in the blood picture and with involvement of one or more parts of the reticuloendothelial system (lymph nodes, liver, spleen). The so-called Felty's syndrome is the latest such syndrome (arthritis, splenomegaly, leukopenia). Felty (1924) himself concluded that the syndrome was probably not a new disease and others have felt that it is merely another pathologic combination

of arthritis and reticulo-endothelial reaction, little different from other syndromes reported by Chauffard (1896), Still (1897) and Herringham (1909), and that a new name is therefore unnecessary. We have noted that Moltke [163] agreed with those who believe that adult or juvenile Still's disease is but atrophic arthritis with a little different physiologic response than usual. Splenectomy has been done occasionally in such cases [4] recently by Hanrahan and Miller (1932) and lately by Craven.[285] The patient whose case was reported by Hanrahan and Miller obtained some relief for at least four months. Craven's patient obtained only transient improvement in the arthritis, leukopenia, and hepatic function. In a similar case Price and Shoenfeld [286] considered sympathectomy, but this was precluded by fatal pericarditis. The spleen in the latter case, and in that of Craven, presented the pathologic picture of chronic infectious splenitis. Price and Schoenfeld concluded that "Felty's syndrome" is not a new disease or syndrome but merely a single, extended pathologic process.

[It should be pointed out again that the pathologic findings in these various combinations furnish considerable support for the theory of infection as a cause of atrophic arthritis.—Ed.]

Thyroidectomy: This has been advocated in selected cases of atrophic arthritis by Duncan (1932) and was approved by Ober [153] if definite hyperthyroidism is present.

Articular bone puncture: The evidence in favor of this procedure as recommended by Mackenzie (1932, 1933) has not been impressive to his fellow-countryman, Ducker.[211]

[The latter, however, has not so treated any cases himself.—Ed.]

Orthopedic procedures: When deformity impends, it is as much the duty of the attending physician, as of his orthopedic colleague, to be familiar with simple home methods of preventing or correcting them. If deformities seem inevitable, it is imperative that the affected joints be kept in the best position for optimal function or for subsequent orthopedic procedures. These positions have again been concisely and diagrammatically outlined by Schrock,[287] McBride [288] and Hench and Meyerding.[237] The various corrective, non-surgical orthopedic procedures necessary for articular rehabilitation of children were surveyed by Green and Ober.[289]

Prognosis. Remissions, Spontaneous and Precipitated. The observations of Nissen and Spencer [152] on the course of atrophic arthritis have been noted. Although many investigators would be inclined to agree with Archer,[146] that advanced atrophic arthritis seems to be incurable by the physician and that nature alone is in control of the outcome, nevertheless the majority will not accept so pessimistic a viewpoint. There is ample evidence that a coördinated program made up of those reasonable measures which an intensive study of the victim's physiologic processes will indicate, if carefully instituted and patiently persevered in, is in time followed by distinct

amelioration, and often by complete inactivity of the disease. Brooks [142] and others have emphasized the length of time over which it is necessary to carry on treatment to accomplish results. To a large extent, the degree of recovery experienced depends on the intelligence of the patient as well as on the skill of his physician.

"There is no panacea and none is needed as statistics show that a high percentage of cases properly treated recover." [166] The chief discontent of all is based, of course, on the fact that treatment often takes so long and requires so much of the patient's time, money and endurance before the final natural or induced remission occurs and the disease becomes finally inactive. As Pern [236] said, "Though the road may wind up hill all the way and the journey take the whole long day, the night will pass and with it its fears and dreads. The dawn will break and with the dawn the mists will melt and full day will bring understanding and with it crippled joints and broken lives will belong to the night that is passed." Rather lyrical but none the less true.

Since sudden remissions are not the rule, Hench [290] was particularly interested in the precipitous remissions induced by intercurrent jaundice in 16 cases of atrophic arthritis and fibrositis. In most instances the jaundice was caused by the toxic action of cinchophen but the marked, generally complete analgesia experienced with the onset of jaundice was in no way attributable to cinchophen, for patients who had simple catarrhal jaundice experienced similar relief. In the majority of cases, marked reduction in swelling and marked increase in motion accompanied the more or less complete analgesia, and the rheumatic process can be said to have suddenly become inactivated. The remissions lasted for variable periods, sometimes only for days or weeks, occasionally months or years. Further investigations are under way to see if the obvious therapeutic implications can be realized so that one can repeat nature's miracle, and provide at will a similar beneficence by the use of some non-toxic accompaniment of jaundice effective in available concentration. These observations have been confirmed by Sidel and Abrams,[291] who noted, with the onset of jaundice, abrupt termination of arthritic pain in four cases, in one of which there was also marked reduction of swelling, stiffness and redness. In two instances the jaundice was of the catarrhal type; in two, it followed the use of oxyl-iodide (cinchophen).

Hypertrophic Arthritis

Incidence. Recent roentgenographic and pathologic evidence (for example, Heine, 1926) indicates that hypertrophic arthritis (the clinical syndrome as contrasted with a roentgenographic alteration) is universally present among persons whose age is more than 45 or 50 years but that it is symptomatically evident in examination of only a very small proportion of its victims—probably 5 per cent. It may very occasionally appear when persons are between the ages of 30 and 35 years, with other evidences of

premature senescence (early grayness of hair; early spontaneous or artificial menopause). In spite of the enormous prevalence of the disease, it is rarely dignified by studies directed primarily to it, but it is usually mentioned only in passing to emphasize some contrasting relationship to, or as a "control" for, atrophic arthritis.

[American studies on the pathologic incidence of hypertrophic (degenerative) arthritis are now forthcoming: Keefer and Myers (1933); Bauer and Bennett (1933).—Ed.]

Symptoms and Course. New data on symptomatology have not appeared. In the discussion on the course of atrophic arthritis as contrasted to that of hypertrophic arthritis, observations by Nissen [151] and Nissen and Spencer [152] on the course of hypertrophic arthritis were noted. In 3 per cent (one case) of 30 cases, course A (early functional restitution) developed; in 70 per cent (23 cases), course B (remissions, relapses, steady decline) developed; no cases followed course C, and 20 per cent (six cases), course D (progressive fairly rapid disability until death).

[As we noted heretofore, the idea that hypertrophic arthritis leads to death is not consistent with the facts.—Ed.]

Roentgenograms and Pathology. No new studies were available for this review.

Laboratory Data. As noted previously herein, the leukocyte count is likely to be lower and the Schilling differential count to be normal in cases of hypertrophic arthritis, as contrasted to alterations in cases of atrophic arthritis.[167, 168] The cell count of synovial fluid in one case of Keefer, Myers and Holmes [11] was: total cells per cubic millimeter, 600; polymorphonuclears 88 per cent, lymphocytes 8 per cent, monocytes 4 per cent.

[A count in one case is of no significance; since so few such counts have been made, however, this case is noted.—Ed.]

Metabolic rates: Among 21 patients who had hypertrophic arthritis of the hips, and who were seen by Kuhns,[292] metabolic rates were low in 18 cases.

Etiology and Pathogenesis. Under general remarks on the etiology of chronic arthritis were noted various ideas concerning the cause of hypertrophic arthritis. Those investigators who stressed the prime importance of infection as a factor are in the minority. The majority recognized tissue-age and trauma as the most obvious causal agents. Few writers were satisfied to consider but one factor responsible for the disease—an interplay of abnormalities is generally incriminated: (1) degenerative tissue-changes incident to age—the progressive, uncompensated catabolism of tissue-senility, (2) long continued trauma above and beyond the ability of articular tissues to repair the "microtraumatic" damage, (3) a circulatory derangement, (4) some nutritional abnormality, (5) an endocrine deficiency, or (6) the factor of infection. Thus Kuhns,[292] from a study of 79 patients who

had hypertrophic arthritis of a hip, concluded that the disease is the product of several factors: trauma, faulty posture, disordered intestinal function, infectious and endocrine disturbances.

[Some of us believe that one major cause exists, the discovery of which will result in a realignment of all other factors into their proper secondary position as precipitating or predisposing, not causal factors.—Ed.]

Factor of tissue degeneration: Because of the age-incidence of the disease, the general absence of the usual signs of an infectious process, the frequent association of the disease with recognized evidences of tissue senility, and particularly because of the degenerative nature of the articular pathologic change, hypertrophic arthritis is considered by most investigators to result from an "altered metabolism" [whatever that may be.—Ed.] incident to age.[175] The theory gains some weight from studies by Bruger and Poindexter,[171] and by Hartung, Greene and Bruger,[172] on the cholesterol content of blood. There was an increase of plasma cholesterol, not explained by the fact that patients who have hypertrophic arthritis tend to be obese. The range among 50 cases was 140 to 340 mg. of cholesterol for 100 c.c. of plasma. The arithmetic mean was 235 mg. (as compared to 195 mg. for the control group and 175 mg. for a group of 50 patients who had atrophic arthritis). Since similar elevations are found in diseases considered degenerative (hypertension, arteriosclerosis, diabetes), an elevation of plasma cholesterol in cases of hypertrophic arthritis suggests that this is also a degenerative disease.

Factor of trauma: Higgins [30] and Swaim [238] wrote of the importance of this factor. The importance of occupation as an inciting agent was stressed by Higgins, who stated that laundresses seem particularly prone to the development of Heberden's nodes.

Factor of circulatory alterations: Pemberton's ideas on the relationship of sluggish capillary circulation and altered tissue nutrition to the causation of hypertrophic as well as of atrophic arthritis are familiar to all. Of probable etiologic importance, he felt, is this combination of circumstances: capillary constriction with sluggish flow; delay in the normal delivery of certain constituents of the blood, especially oxygen and glucose, to certain tissues; partial tissue anoxemia; further metabolic disturbances at least partly responsible for the pathologic changes in, and the symptoms of, arthritis.[196]

Since Wollenberg (1908) launched the "circulatory theory" of arthritis deformans and showed experimentally that interference with the circulation to articular bone was followed by hypertrophy of bone (an experiment more recently repeated by Goldhaft, Wright, and Pemberton, 1930), more obvious evidence of circulatory deficiency, probably from arteriosclerosis, has been sought in cases of hypertrophic arthritis. Of 72 cases, in 78 per cent Nissen and Spencer [193] found arteriosclerosis demonstrated in

roentgenograms of various sites. Of these cases, in 7 per cent the patients were less than 40 years of age.

[As we noted before, anatomic correlation was not shown between the arthritis and the arteriosclerotic vessels.—Ed.]

Kovacs [189, 190] found small capillaries in 28 per cent, a slow blood flow in 53 per cent of his cases of hypertrophic arthritis, with a decrease in number of capillaries near Heberden's nodes. Bick [293] found definite hypertension in 90 per cent and varicosities of lower extremities in 77 per cent of his cases. From certain experiments and philosophic considerations, Bick has concluded that most cases of osteo-arthritis demonstrate clinical evidences of circulatory abnormalities, and that "all investigations on the mechanics of osteo-arthritis point to the peripheral vascular system as the modus operandi of its etiologic forces." The advent of senile involution produces a systemic passive congestion which results in failure of circulation to the cartilage; thinning, erosion and fibrillation of cartilage and hyperplastic reactions in bone result.

[It is difficult to understand how identical circulatory derangements or insufficiency can cause atrophic arthritis in one case, hypertrophic arthritis in another. The two pathologic pictures are totally different. As one of us has stated, one must distinguish sharply between the application of the theory of circulatory deficiency to atrophic and to hypertrophic arthritis.[192] When patellar vessels are ligated and the blood supply is sharply diminished, resulting alterations in bone are chiefly hypertrophic, not atrophic. This is what one would expect if one accepts the recent dictum of Jones and Roberts (1934) that bone undergoes increased calcification if its blood supply is decreased, but it undergoes decalcification if its blood supply is increased. If this is true, the theory of circulatory deficiency would seem much more applicable to hypertrophic than to atrophic arthritis, and in the latter disease one might better search for an augmented, not a decreased blood supply to account for atrophy of bone in atrophic arthritis. Such a state has been suggested as being present in the form of hyperemia and formation of new vessels.—Ed.]

Factor of altered nutrition: In "many cases" Gammon [294] and Archer [146] found decreased sugar tolerance. However, Archer felt that the evidence of obesity, hypertension and endocrine disturbances probably accounted for it. Gammon also mentioned abnormal purine tolerance in many cases.

[Statements similar to this last are frequently made, in general without adequate evidence in support thereof. By the endless repetition of such unsupported opinions, these ideas become fixed in the literature. Exhaustive research has failed to disclose a related purine abnormality.—Ed.]

Endocrine factors: The presence of endocrine abnormalities was vaguely mentioned by many who continued to fail to produce definite evidence of them. Thus, we read that metabolic disturbances "unquestionably play a prominent rôle, as manifested by the gratifying response to reduction in weight and compensation for endocrine deficiencies by the use of thyroid extract and ovarian and pituitary hormones." [173]

[This is another example similar to the one just commented on. It is agreed that reduction of the trauma of obesity is of great importance in hypertrophic arthritis. Therein lies the value of thyroid extract. None but a weight-reducing effect has ever been proved for it, and in a disease presumably the result of catabolism in excess of anabolism, it is difficult to see how the administration of thyroid extract could help matters. The value of other than weight-reducing endocrine substances in this disease remains entirely unproved.—Ed.]

Factor of infection: The ideas of several writers, in this regard, have been noted previously. For example, Brooks [142] expressed the belief that the disease is of staphylococcal origin (no supporting data given). Trauma is usually considered the cause of the symptomatic exacerbations of quiescent or relatively symptomless hypertrophic arthritis. Key [184] expressed the opinion that sometimes this idea is scarcely tenable, and that infection of low grade may produce symptoms in cases of the disease which, like the majority of cases, would otherwise be symptomless.

Because cases of osteo-arthritis and spondylitis osteo-arthritica (atrophic spondylitis) presented but few high antihemolysin titers (in contrast to those of atrophic arthritis) Griffiths [106] looked on the disease as noninfective.

Conclusions on etiology: We can but conclude, as formerly, that the disease is of unknown origin but is obviously conditioned by age and is aggravated, pathologically and symptomatically, by trauma and, some would add, perhaps to a less extent by infection and other less well-defined abnormalities of nutritional, circulatory and endocrine nature.

Treatment. Removal of foci: It has been noted that Steindler [212] found foci of infection in only 17 per cent of his cases and that removal of these foci gave real relief in only 8 per cent of those cases in which it was done. The majority of writers continue to agree that removal of foci does not particularly affect the course of the disease.[148, 295]

Diet: Sladen, Ensign and McColl [195] rearranged the type, and Scull and Pemberton [296] reduced the amount of carbohydrates, ascribing benefit to such dietary measures in cases of hypertrophic, as well as in cases of atrophic arthritis. Tissue edema, also occasionally present in cases of hypertrophic arthritis, may be thus reduced. The majority of writers contented themselves with correction of traumatizing obesity, if present.[121, 175]

Vaccine: These are but rarely recommended [224]; they are generally disapproved.[148]

Histamine: This is recommended by some for hypertrophic, as well as for atrophic arthritis.[232]

[No acceptable data indicating its worth are at hand.—Ed.]

Mecholin iontophoresis: In general, the results of this method in cases of hypertrophic arthritis were no better than those derived from simpler measures.[189, 234]

Blood letting: Kovacs advocated this measure in cases of hypertrophic arthritis in which "a plethoric state and high blood pressure are generally present." [140]

[As a matter of fact, plethora is generally absent according to Sparks and Haden (1932), who found the blood volume 7 per cent below normal in 15 cases.—Ed.]

Physical therapy: The usual physical therapeutic measures were advocated.[235]

Fever therapy: This has proved of little value. The early experiences of Tenney, Berris and King have been reviewed previously.[4] Simpson [22] has treated about 25 patients, with disappointing results. They did not tolerate treatment well, and any relief obtained was transient.

Orthopedic operations: When marked stiffness occurs orthopedic operations occasionally are performed.[297]

Prognosis. Aside from those of Nissen [151] and Nissen and Spencer [152] no new data on prognosis are at hand. Kuhns [292] voiced the general opinion that when adequate therapy and protection are supplied for the joints, progressive deterioration is not inevitable, even among aged persons.

Backache and Sciatica

Space for this review does not permit a synopsis of the voluminous but confusing and often contradictory literature on backache and sciatica, which are symptoms of many paravertebral disturbances and diseases. The editors have failed to recognize much that is particularly new in the year's numerous articles on these subjects, but several informative and representative reports are available on the following subjects dealing with the differentiation of types and causes of backache and the sciatic syndrome: backstrain [298]; postural backache [299]; traumatic backache [9]; postoperative and parturient backache [300]; reflex backache [301]; low backache from disease of facets [302] or from paravertebral muscular insufficiency [303]; sacroiliac strain and subluxation with the treatment thereof by Baer's hyperflexion manipulation [304]; congenital malformations and spondylolisthesis; the relationship of sciatica to narrowing of the lumbosacral disk [305] or to disease (fibrositis) of the pyriformis muscle,[306] and the behavior of the intervertebral disks in tuberculous, typhoidal or specific infectious spondylitis and malignancy.[307] A brief history of backache was given by Wentworth.[308]

These reports again emphasize the importance of thorough physical and roentgenologic examination and the importance of considering all possibilities before making a diagnosis of rheumatism or arthritis without definite evidence of articular disease. Because bony spurs, large or small, are present, one must not assume that the condition is explained; many large spurs are symptomless, small spurs may cause considerable pain, but one must be sure spurs have not long antedated symptoms. In diagnosing a patient's disease, evaluating symptoms and ruling on compensation cases one must use certain physical maneuvers and therapeutic tests. Buckley [309] cautioned that in preparing to testify at a compensation case the physician should remember the dictum "exaggeration is very common—just as common as malingering is rare. Exaggeration is the natural defensive mechanism of

one who fears he presents inadequate external evidence of the pain he feels."

Sciatica. This condition was grouped by Burt [310] thus: 1. Root sciatica (36 per cent of his 140 cases) is most commonly attributable to intervertebral arthritis or strain of the lumbar vertebrae and pressure from new growths. 2. Trunk sciatica (17 per cent of his cases) is attributable to inflammation of the sciatic sheath, primary or secondary to inflammation in the gluteus maximus or pyriformis muscles. 3. Referred sciatica is attributable to inflammation in some structure supplied by the sciatic plexus (45 per cent of his cases).

The general treatment was outlined by Burt and by Yeomans,[311] physical treatment by Wolf [312] and the use of injections of alcohol, quinine-urea or thiosinamine by Thomson.[313]

[The complications and untoward sequelae that may attend the injection treatment of sciatica are not sufficiently stressed in these articles.—Ed.]

The production of 15 to 30 minutes of complete anesthesia by evipan sodium (a barbiturate) for use during the manipulative treatment of sciatica was recommended by Douthwaite.[314]

Spondylitis

There is even more confusion in the clinical, pathologic and roentgenographic differentiation of types of arthritis of the spine than in similar differentiation of types of arthritis of peripheral joints. There is a tendency on the part of some investigators to recognize two main divisions equivalent to atrophic and hypertrophic arthritis elsewhere and then to subdivide each group further. Until better evidence is available, the majority have preferred to ignore subdivisions entirely or to consider them but minor variations of the two main types; namely, atrophic spondylitis (spondylitis rhizomelique or ankylosing spondylitis) and hypertrophic spondylitis (spondylitis osteo-arthritica).

[This viewpoint is favored by us.—Ed.]

Two reports illustrate these differences of opinion: Miller [315] recognized two main types; Doub [316] approved of further subdivisions. Miller considered "atrophic arthritis of the spine" to be synonymous with "spondylitis rhizomelique," and expressed the belief that the Marie-Strümpell type (spondylitis ossificans ligamentosa of Knaggs) and the von Bechterew type (spondylitis muscularis of Knaggs) are variations of the same process, not worthy of particular differentiation. Doub favored Knaggs' separation of atrophic spondylitis under two subheadings: spondylitis ossificans ligamentosa (Marie-Strümpell type) and spondylitis muscularis (von Bechterew type). Another type, called "spondylitis senilis," supposedly a variety of spondylitis muscularis as it appears among elderly persons, was listed by some under atrophic spondylitis, by others under hypertrophic spondylitis.

Atrophic Spondylitis (Spondylitis Ankylopoietica). This is presum-

ably the spinal equivalent of atrophic arthritis and the same in its cause and general treatment. Miller qualified the synonymity by saying, "Rheumatoid (atrophic) arthritis of the spine is usually followed by pathologic changes recognized as spondylitis ankylopoietica. It is perhaps unnecessary to state that a patient with spondylitis ankylopoietica does not necessarily have rheumatoid arthritis of the spine. . . . However, (the latter) leads to (ankylopoietic) changes." Doub, urging further subdivision, stated that spondylitis ossificans ligamentosa and spondylitis muscularis are similar only in that both are characterized by spinal ankylosis and dorsal kyphosis. "It seems rather odd that they should be considered stages of the same process. Their pathology, signs, symptoms and development are quite different, and the etiology as given by most authors is also distinct."

[No original data are given in proof of these statements.—Ed.]

Presumably the differentiation is as given in table 1.

TABLE I

Characteristics of Spondylitis

	Spondylitis ossificans ligamentosa		Spondylitis muscularis
Situation	Spinal column, sacro-iliac joints, hips, shoulders		Not in hips or shoulders
Progression	Ascending type, from lumbar region		Descending type, from cervicothoracic region
Appearance	Thoracic region	Flat, immobile chest; kyphosis	Flat, immobile chest; kyphosis more marked
	Lumbar region	Generally straight	Generally lordotic
Pathology	Vertebral bodies	No marked change	Fusion at anterior margins
	Intervertebral disks	Little or no change	Atrophic, narrowed, may disappear
	Spinal ligaments	Calcification	No calcification
	Facets	Ankylosis through bony proliferation and ligamentous calcification	Not mentioned in current references
	Other areas	More a periarticular, calcifying fibrositis than an arthropathy	Muscular weakness, followed by secondary spinal changes; calcification is bony, not ligamentous

The incidence of atrophic spondylitis outside of special clinics for arthritis is, according to Miller,[315] not very great. Miller cited Schmorl and Junghanns (1932) to the effect that only eight cases were found among 10,000 postmortem examinations. Doub was sympathetic to the idea of

Oppel (1929), of Ballin and Morse (1931) and of others who have included ankylosing spondylitis in the chapter on hyperparathyroidism.

[No new evidence is presented. We have stated previously [4] that the evidence is entirely inadequate for us to adulterate the syndrome of hyperparathyroidism with any of these forms of arthritis.—Ed.]

Nothing new is offered in treatment.

Hypertrophic Spondylitis (*Spondylitis Osteo-Arthritica*). This is similar to hypertrophic (degenerative) arthritis elsewhere in the body and is characterized, early, by flattening of the margins of the vertebral bodies, later by the formation of marginal exostoses or osteophytes, narrowing of the intervertebral spaces and eburnation. Bony ankylosis is not the rule; spurs often impinge but do not unite. The lumbar and midcervical portions of the spinal column generally are involved; the thoracic portion is much less commonly affected, at least symptomatically. The condition has been found, roentgenographically, almost universally to affect patients who are more than 50 years of age (Garvin, 1927). Miller cited Schmorl's statistics on postmortem studies of 10,000 spines and in particular 4,253 macerated specimens. Spinal osteophytes were not found in subjects who had been in the first two decades of life. They were present in 11 per cent of those in the third, in 36 per cent of those in the fourth, in 78 per cent of those in the fifth, and in 93 per cent of those in the sixth decade.

We have commented previously on roentgenographic and postmortem studies of the incidence of hypertrophic arthritis in other joints. The studies of Keefer (1933) on knee joints have been extended by Keefer and Myers who cited age and trauma as causes of the condition and outlined a pathogenesis similar to that reported by Schmorl. To Keefer and Myers,[317] the so-called exostosis represents, however, not overgrowth of bone but flattened portions of the margins of joints squeezed out by pressure.

[This is not the opinion of most pathologists.—Ed.]

The accepted cause of hypertrophic spondylitis is degeneration from tissue-senility and trauma, particularly that incident to man's upright posture. Ely [318] has reiterated his view that this form (spondylitis type II) is attributable to a living non-bacterial organism which causes aseptic necrosis, followed by secondary changes of traumatic arthritis. Judging from his previous papers, he may mean an ameba. He has expressed the belief that the causal organism enters the body from roots of dead teeth and is probably later domiciled in the intestines.

[Ely admittedly never has been able to prove his suspicions. No new evidence is given.—Ed.]

Miller traced Schmorl's ideas on pathogenesis as follows: (1) loss of fluidity, fibrous desiccation and disintegration, first in the nucleus pulposus, then in the annulus fibrosus; (2) thinning and loss of resiliency of disks;

(3) increased mobility of involved vertebrae; (4) impingement of vertebral rims, producing trauma which leads to formation of osteophytes, and (5) increased strain on vertebral ligaments producing periosteal irritation and formation of new bone.

Apropos of the factor of trauma, Buckley and Miller reminded readers of Beneke's (1897) observation that if a man is right-handed the largest lumbar osteophytes are on the left side and vice-versa.

The symptoms originating from nerve roots, which may arise about the head, neck and arms, were listed again by Bisgard[319] (1934). Pseudo-angina pectoris may also originate from cervical involvement.[320]

Nothing new on treatment has developed: Bisgard expressed himself as favoring roentgen therapy. Vernon[321] recommended paralgesia—para-vertebral block with procaine for relief of pain.

The Facet Syndrome

In discussions on pathology of the spinal column, the vertebral bodies and intervertebral disks generally command attention—the facets are rarely noted. The importance of diseased facets in the production of pain low in the back, with or without sciatica, has been emphasized only recently, in 1927 by Putti, and now by Ghormley.[302] The articular facets are the only true joints in the spinal column; they may be affected by acute traumatic arthritis from fracture of them, by chronic traumatic arthritis consequent on narrowing of the fifth lumbar intervertebral space, or less commonly by infection. The common pathologic findings place most cases of arthritis of the facets in the group of hypertrophic (degenerative) arthritis, resulting generally from trauma. Pathologic change of the facets includes degeneration of its cartilages, hypertrophy and eburnation of underlying bone.

The patient affected with the facet syndrome may complain of sudden onset of pain low in the back, brought on by some activity, often trifling in its severity but usually involving a twisting or rotary strain of the lumbosacral region. Sciatic scoliosis and muscular spasm may ensue; until spasm subsides pain may persist. The pains, static in type, can be relieved by assuming a certain posture, or can be exaggerated by assuming other postures; the pain is of a "locking type." Satisfactory demonstration of changes in facets, hitherto impossible, is now possible with the roentgenographic technic of Ghormley and Kirklin; an oblique or three-quarter view is taken.[322] Ghormley advised conservative therapy in the form of recumbency with or without traction; physiotherapy; possibly epidural injections. If these fail, manipulation or long recumbency in plaster of paris casts may be needed, or even lumbosacral fascetectomy, the technic of which Ghormley described. By such a procedure, Mitchell[323] recently provided relief in a case of sciatica in which there were a narrowed fifth lumbar interspace and subluxation of facets. A curious case was reported by Greig.[324] A left perinephritic abscess developed. Remnants of the abscess were discovered at necropsy

16 years later, with adjacent, localized, unilateral ossifying spondylitis. The chain of events was possibly as follows: recurrent inflammation; alternate hyperemia and congestion; repeated, localized, temporary decalcification with subsequent reformation of bone as the hyperemia subsided; and ultimate sclerosis of bone.

[Apparently roentgenograms were not made at any time.—Ed.]

Gout and Gouty Arthritis

Symptoms and Course. A very readable synopsis of current ideas on gout has been given by Lichtwitz [325] who wrote that gout is always a chronic disease, a fact that should be recognized in the first attack of acute gouty arthritis, for attacks of arthritis are merely surface explosions of what, in the interim, is a more or less symptomless, but not necessarily a quiescent, disease. Lichtwitz recognized but did not clarify the entity, atonic gout. Modern gout affects the thin, nervous type of person more frequently than formerly.

Two cases were used by Hench [326] to emphasize several points: 1. A history of acute, recurring attacks, with complete remissions, is of diagnostic importance; complete restitution of articular function after numerous early attacks is one of the most characteristic features of gouty arthritis, of itself almost diagnostic. 2. Joints other than those of the great toe may be affected, and those of the great toe may be long unaffected; in one case, in which 150 attacks took place, only 10 affected a big toe, whereas in the other case, in 20 out of 30 attacks a great toe was affected. 3. Roentgenograms may long be non-specific, even negative. 4. Repeal of prohibition already has been followed by an increase in incidence of gouty arthritis as seen at The Mayo Clinic (alcoholic imbibition being a precipitatory, not a causal, factor).

The provocative effect of a high-fat (220 to 300 gm.), low-carbohydrate (20 to 50 gm.) diet in cases of gout was noted by Lockie and Hubbard.[327, 328] On such a diet, within two to six days, in each of four cases acute gouty arthritis developed. If the diet was maintained, hyperuricemia developed. Ketosis was not sought. A similar diet did not aggravate atrophic or hypertrophic arthritis.

Acute gout occasionally may be precipitated by administration of insulin (Rabinowitch, 1928). In this connection it is interesting to note the provocation of allergic arthritis (symptoms of serum-sickness; not of gout) in the case of a diabetic female after administration of insulin, a phenomenon which, according to the belief expressed by Johnson,[329] may represent an unusual type of insulin allergy.

Associated and Complicating Conditions. Acute and chronic gouty arthritis both have their symptomatic and physical differences—some obvious but others subtle—from atrophic arthritis, although the former may simulate the latter in some regards. The association of gouty arthritis with un-

mistakable atrophic arthritis is very rare according to those of wide experience with both diseases. Cecil[165] reported the association in two cases.

[Both of Cecil's patients undoubtedly had gout, but the diagnosis of atrophic arthritis is based on the presence of fusiform joints and positive agglutination of hemolytic streptococci. The former may occur in gout; the complete diagnostic significance of the latter is not accepted by all. From data given we cannot accept the association as proved in these cases.—Ed.]

Gout of adults not infrequently is associated with blood dyscrasia: pernicious anemia when treatment with liver is being given, leukemia, and polycythemia. Some investigators say gout is merely a symptom of destruction of nuclei of blood cells. Vining and Thomson[330] have reported the association of gout with aleukemic leukemia in the case of a boy aged five years.

[No blood chemical studies were reported.—Ed.]

A case of erythremia, migraine, gout and intracardiac thrombosis was reported by Weber.[331]

Etiology and Pathogenesis. Lichtwitz[325] agreed with the idea that uric acid is nontoxic and not the cause of gout. The symptomatic activity of gout and the production of gouty arthritis do not parallel the degree of hyperuricemia. He favored the allergic theory of gout; allergens are both exogenous (food and drink) and endogenous (tissue substances formed after injuries, surgical operations, sharp vasomotor disturbances). In this connection the opinion of Eaton and Love[332] should be noted: chronic arthritis (especially the atrophic type), may be an allergic disease, with excess of uric acid in synovia and blood acting as the predisposing agent.

[Hyperuricemia is occasionally seen in cases of atrophic or hypertrophic arthritis, but it is the unusual, not the usual, finding. Since the mechanism and significance of hyperuricemia is but little understood, and allergy and allergic arthritis even less clear, these remarks must be considered highly speculative.—Ed.]

Treatment. The patients of Lockie and Hubbard, when placed on a high-carbohydrate (350 to 400 gm.) diet, promptly recovered from their attacks which were induced by high-fat diets. It is advocated, therefore, that patients who have gout avoid fats and accept a generous intake of carbohydrate. The purine-free diet is more highly regarded by the physician than by his patient, according to Lichtwitz, who prescribed it only for four to six weeks after an attack; a low-purine, low-meat diet thereafter. When large tophi are present their removal is indicated to prevent juxtaarticular ulceration, which may necessitate amputation of phalanges, and to relieve the kidneys if possible, according to Hench.[326] Theoretically, removal of large tophi (weighing 10 to 300 gm.) may relieve the kidneys of the work of many weeks or months. These are but mathematical speculations, Hench admitted, and how much relief is afforded the kidney in gout, by removal of large tophi is problematic, since the factors which govern

resorption and excretion of tophaceous material are but little understood. Cinchophen should be used only intermittently and with great caution, according to Copeman [333] and Lichtwitz. However, the use of tolysin (neocinchophen) in moderate doses (5 grains three times a day for four weeks) produced in 120 patients who had "traumatic arthritis" or "infectious arthritis" no functional alterations in liver or kidneys detectable by Stein and Minnich.[334]

[The editors do not favor the use of cinchophen whenever an efficient substitute is available, such as acetylsalicylic acid, in treatment of atrophic or hypertrophic arthritis. It would appear [4] that there is no physiologic equivalent for cinchophen in the presence of gout, and since most cases are not long controlled by diet alone, the careful intermittent use of cinchophen seems justified. The doses of cinchophen, in tolysin, were not great enough or given long enough to justify drawing conclusions on the toxicity of tolysin.—Ed.]

Quick,[335] who expressed belief that cinchophen poisoning is an allergic manifestation, and acute yellow atrophy a special form of Arthus' phenomenon, wrote that the schedule of intermittent dosage (Graham, 1927) is not protective, indeed may favor the development of hypersensitivity.

In the translation of a fourteenth century French manuscript on gout, Saye [336] found a modern note—a statement promising relief from pain but not complete recovery.

Experimental Gout and the Problem of Uric Acid. Spontaneous gout occurred in turkeys raised by Schlotthauer and Bollman.[337] Tophi and hyperuricemia (to 16 mg. per 100 c.c. of blood) were present. Secretion of uric acid varied with the amount of food taken, not with the amount of uric acid in the blood. The latter increased, decreased, or remained unaltered during periods of widely divergent excretion of uric acid. The fertility of eggs from gouty flocks was greatly diminished. Eggs had an increased content of urate, but not in proportion to the concentration in the blood. Factors of sex and age seemed unimportant. Experimental gout was later produced in 20 turkeys.[338] Tophi appeared only in those in which hyperuricemia of 15 mg. per cent developed and remained for at least two weeks.

The provocative effect of a high-fat diet in the cases of Lockie and Hubbard was in part explained by Quick.[339, 340] Excretion of uric acid can be accelerated by various antiketogenic compounds (glucose, glycerol, pyruvic acid, glycine, alanine, aspartic acid, glutamic acid); also by a high-protein diet. It can be depressed by ketosis and by lactic acid, whether fed or produced in excess in the body; also by benzoic acid, phenylacetic acid, and similar compounds. Ketosis probably accounts for the hyperuricemia of fasting, or when a high-fat diet is employed, or in severe diabetes; excess accumulation of lactic acid may explain the high concentration of uric acid in the blood, which often is present in eclampsia, chloroform poisoning, pneumonia, circulatory failure, and other anoxemic states. Retention of uric acid after ingestion of sodium bicarbonate probably is attributable to the corrective formation of excess lactic acid.

[Since the patients of Lockie and Hubbard ingested 20 to 50 gm. of carbohydrate daily, it is doubtful whether ketosis was present because it is very difficult, if not impossible, to produce ketosis with a high-fat diet unless the intake of carbohydrate is less than 15 to 20 gm.—Ed.]

Other interesting studies on the problem of uric acid which can only be mentioned are that by Martin and Corley [341] on the excretion of allantoin and uric acid by dogs on a purine-free and on a protein-free diet, as affected by glycine; the work of Gersh [342] suggesting that in rabbits, at least, uric acid is not eliminated by renal tubules but by glomeruli; the inability of Ranganathan [343] to produce uric acid calculi in rats by causing them to ingest an excess of uric acid; the uric acid content of human and animal lymph, blood, aqueous humor, and cerebrospinal fluid, as analyzed by Walker [344]; and the studies of Pritham and Anderson [345] on the comparative value of various methods for the determination of uric acid in blood.

Hemophilic Arthritis

A brief but interesting historical sketch was presented by Birch,[346] with a summary of accepted clinical and laboratory data on hemophilia, and a restatement of her ideas (1932) on the cause; namely, that it is an ovarian deficiency. This is but theory, and the cause remains unknown. Hemophilia, occasionally occurring when no ancestor has been known to be a bleeder, is called "sporadic" or "spontaneous" hemophilia. Even so it does not arise de novo but is undoubtedly inherited from a recessive mother, according to Boggs [347] who reported six cases of hemarthrosis in brothers. The likelihood of concealed inheritance seemed precluded, as there was no trace of bleeders in five generations of the mother's ancestry. Therefore the writer, scientifically although not gallantly, raised the question of the mother's illegitimacy. It is generally believed that hemophilia does not exist among females (Bauer and Wehefritz, 1926). Foulis and Crawford [348] expressed their inclination to believe that it may, and they presented in evidence the cases of two sisters, members of a known hemophilic family. One sister had a prolonged clotting time, and her two sons were hemophiliacs. The other sister had been in extremis once following extraction of a tooth and recently had had severe postpartum hemorrhage, not of the ordinary type but a vaginal hemorrhage. Purpura was considered unlikely particularly in view of the family history.

[The data were very meager.—Ed.]

From a total of eight cases, Kahn,[349] Rypins,[350] Solis-Cohen and Levine [351] confirmed the presence of articular roentgenographic alterations previously noted.[4] These include: when seen early, distention of the capsule, widening of joint space, an articular shadow denser than that encountered in ordinary synovitis and irregular areas of density (blood pigments) suggesting calcification; seen later, there are spotty destruction of

cartilage, broadening of femoral condyles, widening of intercondylar space, formation of cavities or cysts from subperiosteal or subchondral hemorrhages and fibrous or bony ankylosis. Late roentgenograms may simulate those of tuberculous, atrophic, hypertrophic or other types of arthritis. There is no pathognomonic sign.

Treatment. To Birch, the rationale of whole ovarian extract is obvious: 40 to 120 grains are given daily by mouth, or 50 to 200 rat units are given subcutaneously or intramuscularly, and have afforded best results. Cotton soaked with ovarian extract is applied to open bleeding areas such as dental sockets. One of Rypins' patients " did remarkably well " under treatment with ovarian extract. Others were disappointed with treatment by ovarian hormone (Stetson, Forkner, Chew, and Rich [352]; Brem and Leopold [353]; Tureen [354]). Hemarthrosis was not benefited or prevented, and no related alterations in coagulation time of blood or of urinary estrogenic substances were observed in a total of eight cases in which treatment was with ovarian tissue given orally, or various ovarian extracts, estrogenic substances or theelin given parenterally. The relationship between hemophilia and female sex hormones was doubted.

[Further study is necessary to determine whether the use of ovarian extracts is more potent than the use of other non-specific tissue extracts.—Ed.]

Pituitary extracts were not helpful in one of Birch's cases. MacFarlane and Barnett [355] suggested the local application of sterile solutions of snake venom (Vipera russelli) in a dilution of 1 in 10,000 or even 1 in 100,000 parts. Blood of hemophiliacs which clotted spontaneously in 35 minutes, clotted in 17 seconds when one drop of 1 in 1,000 solution was added to 10 drops of blood. In the dilutions used, toxins apparently have been diluted beyond harm. Older methods of therapy were reviewed by Birch and by Kugelmass [356]: tannic acid dusting powder, application of raw meat or fresh blood, avoidance of disturbing dressings that adhere to wounds, cold applications the first 24 to 48 hours, later warm applications, goat serum given intradermally, transfusion or intramuscular injection of blood; for joints, elevation of the part, absolute rest, application of a posterior splint to prevent contractures, physiotherapy cautiously.

Psoriatic Arthritis

Many cases are being reported in European continental, few in English or American, literature. One case was reported by Sharma,[357] who, vaguely believing that the condition might be of endocrine origin, gave ovarian substance. A month later the psoriasis had cleared up, the joints were " cured," and although psoriasis later recurred, the arthritis did not.

[The data are entirely inadequate to justify conclusions.—Ed.]

Allergic, Metabolic and Endocrine Arthritis

These terms are appearing less frequently to plague the reader. The year's reports included nothing to clarify their vagueness in any way. The possible predisposing or precipitating importance of such factors as allergic reactions to food (we have discussed bacterial allergy elsewhere), or metabolic or endocrine abnormalities, is worthy of consideration and has been touched on by many investigators, most directly by Johnson [329] in his description of allergic arthritis from insulin, by Eaton and Love [332] in their discussion of the relationship of chronic arthritis and hyperuricemia to allergy, and by Cawadias,[358] who concluded that, although chronic rheumatism is a disease which exhibits important metabolic disturbances, it is not characterized by one consistent, classifiable metabolic derangement as is diabetes.

Diseases of Muscles and Fibrous Tissues (Including Fibrositis and Muscular Rheumatism)

Fibrositis. To some this term is merely an impressive name for any vague ache or pain in the neighborhood of muscles or tendons. To others it is the name of a definite pathologic condition, which is an inflammatory exudation in and hyperplasia of white fibrous tissue anywhere in the body, acute or chronic in type, characterized by formation of nodular indurations appearing in various sizes, situations, and manifesting varying degrees of tenderness. Some accept an anatomic differentiation: intramuscular, fascial, bursal, perineural (of which sciatica is often a type), capsular, periarticular, or subcutaneous (panniculitis).[359, 360] Since an inflammatory reaction in fibrous tissue occurs in rheumatic fever and various types of arthritis, Jones [361] would include them also under the general term, and would speak of "fibrositis of rheumatic fever," of "gout," of "rheumatoid arthritis," or of "osteo-arthritis." In general, however, the term is limited to diseases of periarticular and nonarticular structures. Some writers use clinical or etiologic terms: "traumatic," "infectious," "toxic," "senile fibrositis." [362, 363] The nomenclature of fibrositis thus reveals the same gropings for order amid confusion, the same general etiologic alignments, which exist in arthritis.

Etiology: The exact cause is unknown. That trauma of overexertion (exercise or fatigue) can produce the condition seems clear, but traumatic fibrositis or myositis must not be diagnosed in a haphazard manner. A number of conditions may masquerade as traumatic fibrositis or "charley-horse." Elsom [364] listed them: simple contusions, muscular strain or rupture, actual myositis with or without calcifying hematoma, periostitis and tenosynovitis. Other presumed causes are chilling or dampness; streptococcal infection; bacterial toxins; "bowel toxins"; and acid by-products of fatigue, especially lactic acid. Some consider the condition to be neuralgia of sensory nerves; others believe it is merely a manifestation of neurasthenia.[6, 359, 360, 362, 363, 365] Many writers are very definite in their opinions,

vague in their terms. Thus, Albee was certain that fibrositis is caused by toxins, particularly those derived from the colon, but he wrote of the condition occurring with the gouty diathesis, with excess of uric acid, with cirrhosis of liver, and so on, and he used estimations of the histamine content of the stools as an index of toxicity.

[Not the least evidence of any sort concerning etiology is offered by many of these writers.—Ed.]

Symptoms: These may be acute or chronic and may include muscular tenderness and stiffness; muscular spasm (if acute); tenderness over insertions of tendons; small, tender indurations, or actually palpable nodules. Symptoms are exhibited particularly when affected tissues are put on a stretch. The regions chiefly affected are muscular and fibrous tissue about the shoulders (capsulitis) and in the occipital or suboccipital regions, but particularly in the lumbosacral regions (gluteal and hamstring muscles). In the situation last named, which he felt was the major site, Albee wrote that the left side was affected 10 times more often than the right.[363]

Pathology: The studies of Stockman [365] constitute almost the only definite information we have on pathology, and even these were subject to the dubious inquiry of some.[277] To some writers nodules are very elusive. Others find them without difficulty.[359] At first there is merely a very low grade of inflammatory fibrous reaction, with exudation. Later the exudate may organize, and nodules and indurations may appear.[365] In Pennington's cases sensitive nodules were found most frequently in the gluteal muscles, next most frequently in muscles about the shoulders, and less frequently in intercostal or paravertebral muscles. Almost 40 per cent of the gluteal nodules were symptomless. From the fact that such nodules are found so often in normal persons he deduced that fibrositis can be a transient, functional change from overuse of muscles. A second type of fibrositis is the " pathologic form " which may or may not be infectious. Fatigue, loss of muscular resiliency, chilliness, and vague muscular pains are almost universal in senility—signs of senile fibrositis so common that the term " senility " may be said to be synonymous with " fibrositis." In the other forms, the functional pathologic changes are transient, correctable and reversible. In the senile form, they are permanent, according to Pennington.[362]

Treatment: Proposed methods of therapy concern (1) elimination of foci of infection or of toxins, (2) attention to painful muscles, (3) elimination of sensitive nodules. Albee wrote that he relied on colonic irrigations; acidophilous milk; a diet low in residue and in meat; substitution of lactose for table sugar to reduce production of bacteria and toxin in the bowels. Some rely strongly on physiotherapy, but Stockman expressed the view that although heat is of some service, spa-therapy is useless. Some urge light massage, others insist on firm massage over the nodules as the only way to relieve the condition. If the nodules cannot be dispersed one can " render them hard, callous and insensitive " by massage.[365, 366] Young,[277] however,

found it "difficult to understand how fibrous nodules can be exorcised by massage." To increase excretion of lactic acid, general sweating was urged by Pennington. Some use intramuscular injection of quinine and urea hydrochloride into the tender spots.[367] Histamine can completely cure the condition, according to Mackenna.[233]

[Our information on fibrositis or muscular rheumatism is much more incomplete and contradictory than is the case with other types of rheumatic disease. It is indeed curious that excellent pathologic data are at hand on arthritis, in which affected tissues are much less available for biopsy than are those involved in fibrositis. Until chemical, pathologic and bacteriologic studies on fibrositis are extended, little hope can be entertained for clarity. Practically all articles on the subject give evidence of considerable copy-work; Stockman is one of the few, if not the only, writer who speaks with authority; he at least has made a good beginning. The discussions of most of the writers are highly theoretical, and their treatment uncontrolled.—Ed.]

Epidemic Myositis or Pleurodynia (Devil's Grip; Bornholm Disease). Four reports tell of a recent epidemic of this disease along the Atlantic seaboard of this country and in Yorkshire, England.[368 to 371]

Other names for the condition are "myositis acuta epidemica" and "devil's chitch." Eighty cases are included in the four reports. It is an acute infectious disease of unknown cause, characterized by an abrupt onset of excruciating pain in the chest, epigastrium, or along diaphragmatic attachments; fever; aggravation of the pain on deep respirations and movements of the trunk; disappearance of fever in four to 48 hours; in most cases recurrence of pain and fever after two or three days; invariable recovery without sequelae; occurrence among otherwise healthy persons of either sex, especially children; absence of significant pulmonary or pleural signs; a variable leukocyte count (17,000 to 3,000 per cubic millimeter of blood); and often leukopenia. No reports on studies of the pathology are available. The condition may be mistaken for early acute pneumonia or for an acute abdominal condition. Laparotomy often is performed by mistake. Absence of vomiting is of diagnostic help. Treatment is that of acute pleurisy: isolation of the patient, rest, analgesic drugs, reassurance.

Myositis Ossificans Progressiva. Only about 150 cases are recorded. Two have been reported recently.[372, 373] The classical findings were present and do not need repetition here.[4] Interesting roentgenograms were included, and the difficulty of early diagnosis, when roentgenograms are negative, was stressed.

Bursitis

As we have noted, bursitis is pathologically a form of fibrositis. However, it may be considered in a separate division here.

Subdeltoid or Subacromial Bursitis. An inflammation in the general region of one of these bursae generally takes the name of the adjacent bursa. The calcareous deposits which often occur, however, are not in the bursae as a rule but in the supraspinatus tendon and, according to Gwynne and Robb,[374] probably result from tears of the insertion of the supraspinatus

muscle. Grossman [375] has reviewed 375 cases and Rogers [376] 100 cases. Grossman expressed a preference for the term " periarthritis," which Rogers rejected, since there is insufficient evidence that infection is present. The usual symptoms are recounted and the usual ideas on cause are held—trauma and infection.[377] We are reminded that the calcareous deposits are often transient, and that the condition generally responds to conservative treatment. Aspiration is advised by some.

Prepatellar Bursitis and Ganglion. In three painful cases of the former and 10 of the latter, the condition was inactivated by Eising [378] and by Kaplan [379] with a very few injections of sodium morrhuate. This substance should not be used if the bursal sacs connect with joints or tendon sheaths.

Iliopsoas Bursitis. This is an unusual affection, sometimes difficult to diagnose. In two cases in which trauma was a factor cure was brought about by Ramage and Morton [380] by excision.

Information on the development and structure of bursae is all too meager. Two reports provided data thereon. Since he found no subcutaneous olecranon or prepatellar bursae in fetuses, Black [381] expressed the belief that they develop after birth. Neither subfascial nor subtendinous bursae are present in fetuses but subacromial bursae are. Chandler [382] found iliopsoas bursae present before birth and rarely absent in adults. In 15 per cent of cases, a communication between adjacent bursae and the hip joint exists; this communication is not the result of development but is produced by friction of the iliopsoas tendon.

Miscellaneous Conditions

Lymphatic Leukemia Resembling Rheumatic Fever. This condition occasionally is seen. Articular symptoms resembling those of acute rheumatic fever may be prominent in cases of acute leukemia of children. The literature was reviewed by Sutton and Bosworth,[383] who presented the case of a child 32 months old. At first fever and swollen joints were associated with enlarged nodes but not with an enlarged liver or spleen. Blood counts were normal. A diagnosis of rheumatic fever was entertained without satisfaction since salicylates were ineffective and carditis was absent. Some months later the liver and spleen became enlarged; biopsy of a lymph node confirmed the diagnosis of leukemia. Permission for necropsy was refused.

Lipomas of the Articular Capsule. These were successfully removed from three patients by Ghormley.[384]

Calcification in Fat Pads about Joints. This was noted by Ferguson [385] in four cases.

Physiology of Articular Structures

Studies on the fundamentals of articular physiology are indeed meager. The viscosity of synovial fluid is attributable to its content of mucin. When this is removed the viscosity drops to that of a simple exudate. Studying

lubrication of joints of horses, Jones,[386] an engineer, concluded that the coefficient of friction of a joint that has dried is nearly 14 times as high as when it is lubricated by synovial fluid or normal saline solution. A joint of which the surfaces are not lubricated is quickly destroyed when worked under a light load. It is imperative to study the problem of lubrication in joints of human beings in order to understand arthritic changes.

From his studies on the joints of rabbits and of human beings Kuhns[387] concluded that lymphatic structures are as abundant as are small blood vessels in the tissues lining joints, especially in synovial membrane. Lymphatic drainage of the joints of the lower extremities is through deep lymphatic structures to the popliteal, deep femoral and iliac nodes. Synovitis prevents lymphatic absorption of material larger than molecular size; obliteration of lymphatic structures occurs with chronic inflammation. Kuhns and Weatherford[388] have shown that colloidal and particulate matter may be carried to joints from body tissues and from the intestines through the action of cells of the reticulo-endothelial system. Such transported substances are stored in histiocytes in subsynovial villi. Large amounts are stored in bone marrow; lesser amounts in intermuscular septa and articular fat pads. Mild inflammation in articular tissues tends to increase the deposition of injected substances. Local blocking of the reticulo-endothelial system is transitory and ineffective in preventing deposition of colloidal and particulate matter injected elsewhere.

The effect of immobilization of normal joints is controversial. After experimental immobilization of the ankles of dogs for from one to three months, Ely and Mensor[389] noted the following: frequent periarticular swelling, and thinning, irregularity, fibrillation, at times fibrin plaques and vacuolization of cartilages (but no fibrous adhesions) between the joint surfaces, and some encroachment on, and substitution of, cartilage by connective tissue.

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BOOKS 1934

The following books appeared during 1934 but are not reviewed herein.

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The chairman of the editorial committee for this review will welcome the receipt of reprints from authors of current (1935–1936) articles which will greatly facilitate the preparation of subsequent reviews.

CASE REPORTS

VENTRICULAR COMPLEXES OF THE BUNDLE-BRANCH-BLOCK TYPE ASSOCIATED WITH SHORT P-R INTERVALS *

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IN recent years a number of electrocardiograms have been reported possessing a shortened P–R interval and a bizarre, widened QRS complex of the type usually associated with an asynchronous activation of the two ventricles. Such cases have been described by Wilson,[1] Wedd,[2] Hamburger,[3] Pezzi,[4] Wolff, Parkinson and White,[5] Holzmann and Scherf,[6] and Wolferth and Wood.[7]

The present report is concerned with an electrocardiographic study of a similar case with some further evidence relevant to the underlying mechanism.

CASE REPORT

A. N., a male, aged 44 years, a patent attorney by occupation, was seen by one of us in September 1932, following his rejection by an insurance company because of an abnormal electrocardiogram. Previously his only complaints referable to the heart were occasional attacks of palpitation since the age of six years, unassociated with effort or excitement, appearing suddenly, and lasting for a few minutes. During the attack his pulse was very rapid but regular, and he discovered early that he could terminate the palpitation by holding his breath.

Examination disclosed a well developed adult male. The heart was regular, rate 82; sounds were clear, and there were no murmurs; blood pressure 122 systolic and 80 diastolic. Fluoroscopic examination revealed the heart inclined transversely, but otherwise normal in contour and size.

Electrocardiographic Study. The first electrocardiogram, taken in September 1932, showed a normal sinus rhythm with a rate of 80 per minute. The P-waves were upright in all leads but very close to the ascending limb of the R-wave (P–R interval 0.12 sec.). The QRS complex was widened, being 0.15 sec. in duration and splintered at its apex. The terminal deflection was oppositely directed to the main deflection, the latter being upright in the three leads and similar to the type of complex seen in left bundle-branch-block (new classification). (Figure 1.)

Despite an electrocardiogram usually associated with, and indicative of myocardial damage, it was thought, in view of the apparent good health of the patient, that the electrocardiographic alteration was not the result of organic involvement. Quinidine sulphate, gr. III q.i.d., was given for three days, and another record was taken. The latter showed a definite change from the first (figure 2, A). In all three leads, the abnormal complex had been replaced by normal R-waves associated with lengthened P–R intervals. Except for a left axis deviation, the electrocardiogram was normal in contour. Comparison of the two types of complexes revealed that the

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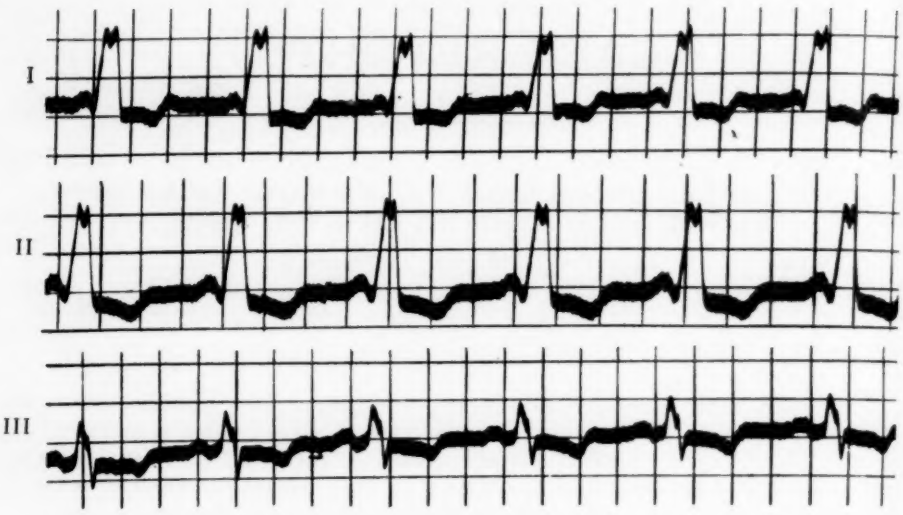

FIG. 1. Usual type of electrocardiogram with short P–R interval and wide QRS complex Time, one-fifth second. 1 cm. = 1 millivolt.

FIG. 2. *A*. Effect of quinidine medication—normal P–R interval and QRS complex present in the three leads.

B. Effect of subcutaneous injection of atropine sulphate, gr. 1/50. Increase in heart rate noted with no change in contour of QRS complex.

C. Effect of digital pressure applied to carotid sinus. Decrease in heart rate noted with no change in contour of QRS complex.

distance from the beginning of P to the end of the QRS wave was approximately the same in both the normal and abnormal groupings (0.274 to 0.279 sec.); and the contour of the P-wave was similar in both.

In order to be certain that the changes recorded in the second tracing were not merely coincident with the quinidine medication, the latter was discontinued and one week later another electrocardiogram taken. This showed only the abnormal type

of QRS complex together with the short P–R interval. At two other periods, quinidine was again administered with approximately the same effect as in the above instance. The withdrawal of the drug always resulted in the return of the abnormal type of curve. At times without any treatment a spontaneous transition from the abnormal complex alone to alternate grouping of abnormal and normal complexes occurred (figure 3).

In the course of one examination the effects of exercise, digital pressure on the

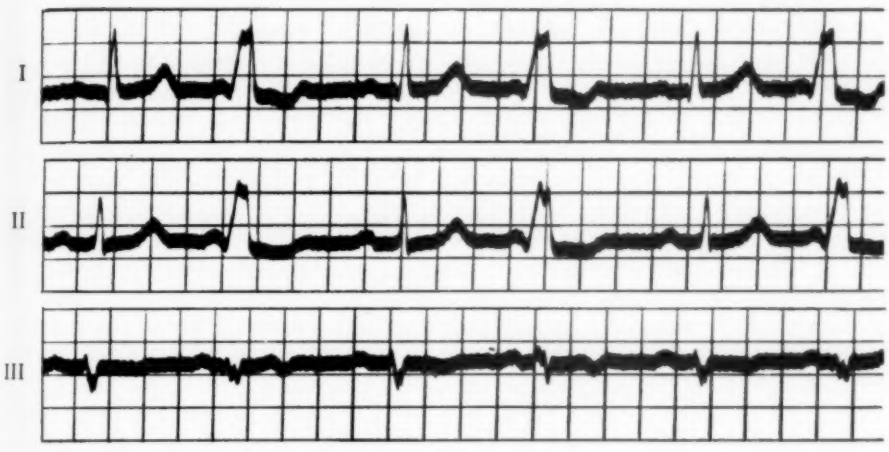

FIG. 3. Electrocardiograms showing alternation of normal and abnormal groupings.

carotid sinus and the subcutaneous injection of atropine sulphate were studied (figure 2, B and C). The rate decreased with carotid stimulation and increased after atropine and exercise. There was no change in the time relations and contour of the abnormal groupings. Electrocardiograms taken at intervals up to the present still reveal one or the other of the above states, but at no time except during quinidine medication have normal groupings been present more often than every other cycle. Unfortunately, no records were obtained during any of the attacks of paroxysmal tachycardia.

DISCUSSION

Twenty-eight cases possessing short P–R intervals associated with widened QRS complexes are described in the literature. The patients were all comparatively young and in only a few could an abnormal cardiovascular history be obtained. However, many had suffered from paroxysms of tachycardia, auricular fibrillation, or flutter.

Recently Wolferth and Wood reported nine such cases and reviewed the previous attempts to explain the mechanism. They further presented an hypothesis based upon the assumption that an aberrant conduction tissue connection (i.e., one besides the Bundle of His and its two branches) was present between the right auricle and right ventricle in these patients and that it was functionally able to conduct impulses. Such a structure has been described by Kent [8] (Bundle of Kent), who presented histological evidence of the existence of a muscular connection between the right auricle and ventricle in the lateral wall. He demonstrated further that when all the structures which connect the auricles and

ventricles in a mammal are severed with the exception of this bridge of tissue, impulses still may be conducted from auricle to ventricle resulting in response of the latter.

In some of Wolff, Parkinson and White's series, factors producing inhibition of vagal impulses brought about a transition to normal. Wolferth and Wood, and Holzmann and Scherf found on the contrary no change under similar conditions. In our patient also, exercise, carotid sinus stimulation, and atropine had no effect upon the characteristics of the abnormal grouping. On the other hand subsequent to the administration of quinidine a normal electrocardiogram was obtained. This drug decreases the rate of impulse spread through conduction tissue as has been noted by numerous investigators, among them Cohn and Levy,[9] Lewis,[10] Schott,[11] Wolferth,[12] and Korns.[13] If we assume therefore that the Bundle of Kent is able to conduct impulses in these patients (as have Wolferth and Wood, and Holzmann and Scherf), a further assumption is reasonable that this tissue, which ordinarily does not have the properties of irritability and of conductivity as highly developed and as well stabilized as the Bundle of His, responds more markedly to depressants like quinidine. Following its administration the impulses tend to be conducted through normal channels. On withdrawal of the drug, the refractoriness of the Bundle of Kent again diminishes and impulses are conducted over it. Measurements made on the normal grouping over a period of three years consistently revealed a prolonged P–R interval (0.222 sec.). Since such an increase is usually the result of a decreased rate of spread through the auriculo-ventricular node, it can be assumed that this is the explanation here. This may in part account for the fact that the effective impulse in most instances is the one traversing the aberrant pathway.

It seems likely that under these conditions the Bundle of His is able to conduct impulses and does so, but when the abnormal complex occurs, the conduction wave passes over two pathways: (1) via the Bundle of Kent, hence reaching the right ventricle prematurely, and (2) via the Bundle of His and its two branches. However, the impulse arriving at the right ventricle by way of the normal route (right branch) finds the ventricle already activated and therefore refractory. In the case of the left ventricle there is evidently a race between the impulses spreading down the left branch of the Bundle of His and those spreading across the septum from the prematurely activated right ventricle.

Summary

An electrocardiographic study of a case is presented possessing ventricular complexes of the bundle-branch-block type associated with a very short P–R interval.

The effects of carotid sinus stimulation, exercise, atropine and quinidine upon the abnormal electrocardiogram are described.

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EXCESSIVE SMOKING AS A POSSIBLE PRECIPITATING FACTOR IN DIABETIC GANGRENE; WITH A CASE REPORT*

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Tobacco smoking became of interest to me as a result of the work by Wright and Moffat [1] who found that smoking produced in the great majority of normal individuals a marked drop in the surface temperature at the tips of the fingers and toes, and frequently a slowing and stoppage of the blood flow in the capillaries of the nail fold. Shortly after their paper was published I saw a young man with diabetic gangrene who gave a long history of smoking a great many cigarettes each day. The case of this man is recorded to suggest that excessive smoking may be injudicious for the diabetic and even may be a factor in helping to precipitate fatal gangrene.

Mr. S. B. was a Jewish business man, 34 years old. He entered the hospital on August 11, 1934, complaining of non-healing gangrene of the right foot. His family history was striking in that his mother died of diabetes at the age of 34 and a sister, now 29 years old, has had diabetes for several years. He had been married for six years and his wife and one child were living and well. He began to smoke at the age of 17 and used 30 to 40 cigarettes a day up to two years ago when he started to smoke more heavily. Since then he has smoked 40 to 80 cigarettes a day, a daily average of about sixty. For the past three years he has noticed at times on exertion numbness and tingling in his right leg. Three years ago he had weighed 223 pounds; but his weight had decreased to 150 pounds when he came under observation.

He was always well until 1931 when he began to feel easily fatigued and noticed that he was losing weight. His diabetic sister recognized the possible significance of these symptoms and got him to visit a doctor who confirmed the diagnosis of

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From the Medical Clinic of the Peter Bent Brigham Hospital.

diabetes. At first the patient was treated with diet only, but after three months he began to take, in addition, 10 units of insulin three times a day, and for a year remained sugar free. He then grew careless and omitted the insulin for a time, but his symptoms returned so that he resumed treatment.

About eight months before entry to the hospital he began to have a noticeable amount of pain in the back of his right leg when walking. At first the pain was trivial but as time went on it became more severe and more frequent. Finally he could walk only for half a block before pain would compel him to stop. He had no pain in bed at night.

About four months before entering this hospital a small ulcer developed on the right little toe. There was no history of any antecedent trauma. He was then hospitalized elsewhere for 10 days and while in bed another ulcer appeared spontaneously on the sole of the right foot. After this period of rest he got up and about and was able to walk a short distance with crutches. The ulcers, however, failed to heal. Four weeks before entry to this hospital he noticed that these ulcers had become black and foul with a purulent discharge and gradually they became so large and uncomfortable that he took to his bed, and entered our institution for treatment.

His general examination was not remarkable except for evidence of loss of weight and gangrene of the right foot. The blood pressure was 100 mm. of mercury systolic and 60 diastolic.

The Wassermann and Hinton tests were negative. The hemoglobin was 94 per cent (Sahli), the red blood count 5,030,000, and the white blood count ranged from 25,000 to 13,000. The blood cholesterol was 185 and 140 mg. on two occasions and the blood sugar varied from 276 mg. to 160 mg. The patient had rare insulin reactions, but no blood sugar determinations were made during them. The urine was essentially negative and it seldom contained even the slightest possible trace of sugar even when the blood sugar was elevated.

The radial arteries were not sclerotic but very soft and easily compressible. The temporal and retinal arteries were normal. The pulsations in the dorsalis pedis artery were present in the left foot but were absent in the right. The popliteal pulse was felt on the left but not on the right. The right foot showed swelling and redness on the lateral aspect. The small toe was black. On the sole of the foot there was an ulcerated area about 8 cm. long and 4 to 6 cm. wide over which the skin was black, crusted, indurated and somewhat peeling. Beneath the crustation there was a foul purulent discharge. Around this area of gangrene the skin was red, angry and edematous. There was also a small ulcer over the external malleolus which was almost completely healed.

Because of the patient's age there was doubt as to the underlying cause of the gangrene. In the previous experience of this hospital diabetic gangrene has been encountered only once in so young a patient. This was a man of 32 who developed gangrene apparently as the direct result of trauma and superimposed infection.

At first it was thought that obliterative endarteritis (Buerger's disease) might be playing a part. However, a number of tests were made which tended to exclude such a diagnosis. Roentgen-rays of the feet, legs and thighs showed an osteomyelitis involving the distal end of the fifth metatarsal and the proximal end of the proximal phalanx of the right small toe. In addition, there was marked calcification of the arteries of the feet and of the posterior tibial arteries of the legs up to the level of the proximal end of the fibula.

Oscillometric studies of the arms and legs gave normal tracings over the arms and the left leg down to the lower part of the calf. In contrast, on the right side there was decrease of the amplitude of the oscillations over the thigh and practically absence of oscillations from just above the knee downwards. This indicated a very poor circulation on the affected side.

FIG. 1. Views of gangrenous foot of Mr. S. B., a diabetic patient.

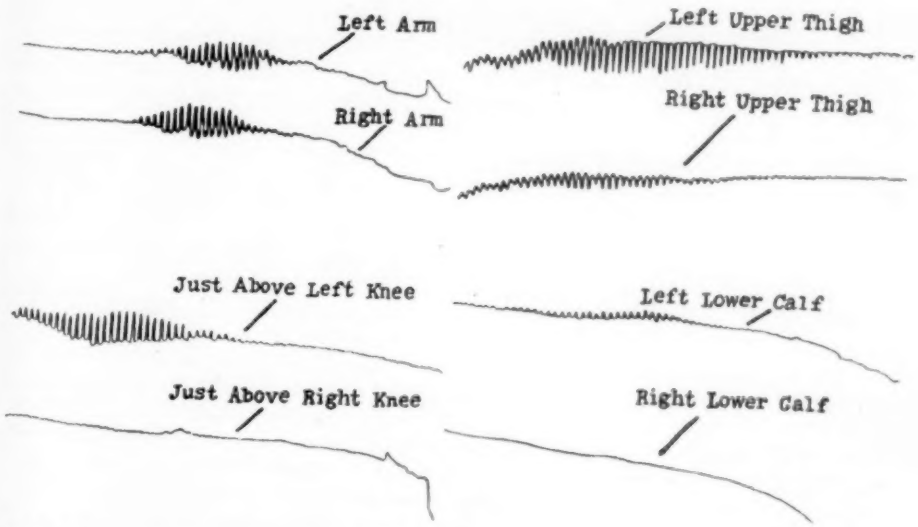

FIG. 2. Oscillometric tracings of the arms and legs of a patient with diabetic gangrene, who smoked on an average of 60 cigarettes a day.

Skin temperatures of the legs were determined with a thermocouple at frequent intervals during a control period until the temperatures remained constant and subsequently during a period of two and one-half hours while the patient was smoking cigarettes continuously. During all that time the patient lay flat in bed in a small room at a constant temperature. The temperature readings were taken at the tibial tubercle, the anterior ankle and the base of the great and small toes. Tobacco smoking produced a gradual decrease in the temperature at the various points during the

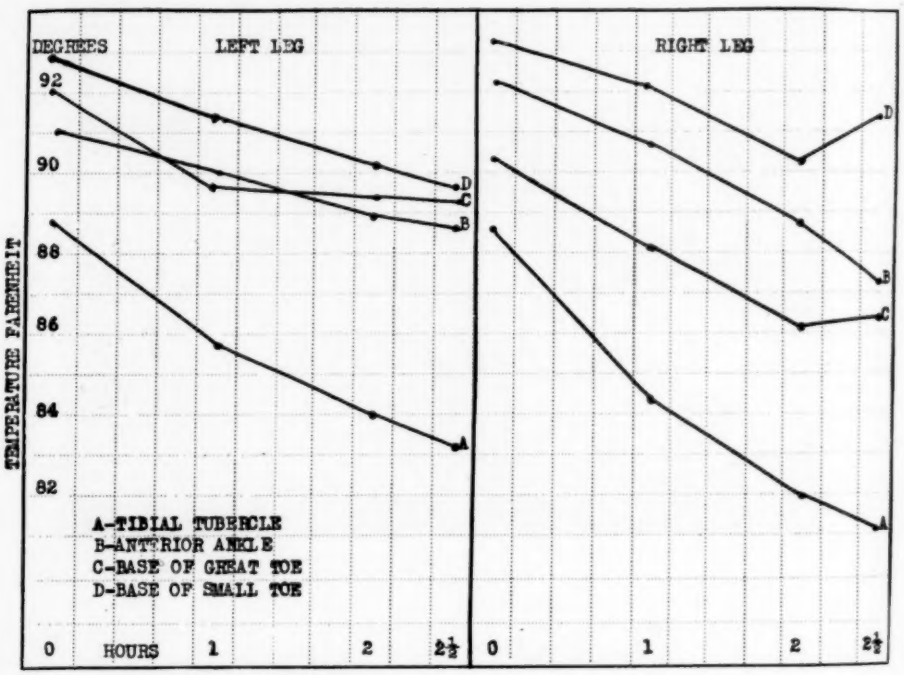

FIG. 3. Skin temperatures of legs of Mr. S. B., a diabetic patient with gangrene of the right foot, while smoking cigarettes for 2½ hours.

period of observation. The maximum drops in temperature occurred over the right and left tibial tubercles and these amounted to 7.1 and 5.3 degrees F. respectively. The decrease in temperature at the other points was less striking. In Wright and Moffat's cases using tobacco, the average drop in skin temperature was 5.3 degrees F. in one hour; the maximum drop was 15.5 degrees F. However, their experiments were conducted on normal individuals.

The patient was given a diet of 150 gm. carbohydrate, 70 gm. protein and 80 gm. fat and 15 to 20 units of insulin three times a day before meals.

The leg was treated conservatively with a heat cradle and the wounds were kept clean. The foot improved and the toe became demarcated. However, in two weeks there developed suddenly a rise in temperature and some lymphangitis of the right leg. A mid-thigh amputation seemed indicated and was performed at once, and the patient progressed very satisfactorily until the ninth day postoperatively when the temperature again rose suddenly and the wound broke down and became infected. The infection progressed and invaded the subcutaneous tissues, producing necrosis of the fascia and muscle over the entire stump. Subsequent operations on the hip failed to be helpful and the patient died on October 10, 1934.

The essential pathological changes in the amputated leg consisted in a thrombosis of the posterior tibial artery. The clot filled the lumen of the vessel and extended from its origin to the region of the external malleolus. It was well organized and was evidently of long duration. Distal to the clot the plantar arteries and the peroneal artery showed considerable atheromatous change. The popliteal artery was not remarkable. Microscopic examination of sections from various parts of the arterial tree of the limb showed arteriosclerotic lesions of varying type. In some of the smaller vessels occasional fibrinous thrombi were encountered. However, the general picture was that of arteriosclerosis and not of thromboangiitis obliterans.

The findings of the postmortem examination were otherwise irrelevant. There was extensive infection of the right hip and an abscess in the right side of the pelvis which extended around the rectum and was in direct connection with the muscles of the anterior thigh. Bronchopneumonia also was present in both lungs. The blood vessels in various organs and other parts of the body were in surprisingly good condition.

Comment

It is of practical interest to attempt to trace the etiology of the gangrene in this case. Certainly the fundamental lesion, as usual, was arteriosclerosis with superimposed thrombosis and infection. In line with the work of Wright and Moffat it is not unreasonable to suggest that the excessive use of tobacco by this patient may have been an important factor in precipitating the gangrene. The lowering of the skin temperature after the use of tobacco is thought to be caused by a slowing or stoppage of the circulation in the capillary bed. Such an effect in an extremity with an already diminished arterial blood supply may well play a considerable rôle in the early development of gangrene. Although the greatest drop in temperature observed after smoking was not more than 7.1 degrees Fahrenheit and hence not as marked as in some of the normal individuals used by Wright and Moffat, nevertheless it is possible that such a fall in temperature so induced, day in and day out over a long period of time in an individual with marked arteriosclerosis, was very harmful.

Since now it is known that the excessive use of tobacco produces definite effects on the peripheral vascular system, it will be of value in the future to investigate carefully the history of excessive smoking in diabetic patients. Diabetics who are ardent smokers should be advised moderation in smoking, since if they will avoid this deliberate insult to a peripheral circulation which already is likely to be diseased and easily vulnerable, they may thereby escape the vicissitudes of unnecessary gangrene.

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EDITORIAL

THE RÔLE OF THE LIVER IN HEMOPOIESIS

THE rôle of the liver in hemopoiesis has aroused increasing interest since the discovery by Minot and Murphy of the curative action of liver when fed to patients with pernicious anemia. It is now well established that liver contains some substance necessary for normal red cell production, which is produced in the normal body, but is lacking in pernicious anemia. A deficiency of this material results in an arrest of the maturation of the red blood cells and in the delivery into the blood stream of cells which are abnormal and functionally defective.

The work of Cohn et al., of West, and many others has shown that chemically this anti-anemic principle of liver is a relatively simple substance quite distinct from the vitamins, proteins and other nutrient materials present in liver. The development of methods of purification by Gänsslen, and by various American workers, which permit intramuscular and even intravenous administration, is of great practical importance as well as of theoretical interest.

We owe to the work of Castle and his associates the first clear insight into the nature of the deficiency in pernicious anemia, as well as the source of the active substance. The action of some ferment-like constituent of normal gastric juice, the "intrinsic factor," on some substance present in certain foods (muscle meat, yeast, etc.), the "extrinsic factor," results in the production of a new substance which, after absorption by a patient with pernicious anemia, acts like liver extract in stimulating a reticulocyte crisis and a rapid production of red blood cells. The gastric juice of patients with pernicious anemia shows a lack (or a great reduction) of this intrinsic factor.

The fact that liver extract is also therapeutically effective in such diseases as tropical sprue, the "hemolytic" anemias of pregnancy and fish tape worm anemia, which show a macrocytic hyperchromic anemia morphologically similar to pernicous anemia, has led some to the generalization that macrocytosis is an indication of some disturbance in the production (or utilization) of this anti-anemic principle of liver. This assumption has received some apparent support from the observation of macrocytic anemia in some cases of advanced liver disease (Wintrobe and Shumacker,[1] Goldhamer et al.,[2] etc.).

Intensive study of these various diseases has shown that the conditions giving rise to the anemia may be complex: in some cases of sprue, the intrinsic factor is absent, as in pernicious anemia. In others the intrinsic

[1] WINTROBE, M. M., and SHUMACKER, H. S., JR.: Occurrence of macrocytic anemia in association with disorders of the liver, Bull. Johns Hopkins Hosp., 1933, lii, 387.

[2] GOLDHAMER, S. M., ISAACS, R., and STURGIS, C. C.: The rôle of the liver in hemopoiesis, Am. Jr. Med. Sci., 1934, clxxxviii, 193.

factor is present, and another explanation must be sought. In some cases of sprue and tropical anemia feeding large amounts of vegex or marmite (autolyzed yeast) relieves the anemia, and a lack of the extrinsic factor seems to be responsible for failure to form the active substance. In some cases of sprue, idiopathic steatorrhea, etc., deficient absorption seems to be the explanation. The intrinsic factor is present, oral administration of marmite or liver is uncertain in its effect, but parenteral injection of liver extract is highly effective.

In the case of anemia in disease of the liver, it is natural to assume that there is an inability of the liver to store, or possibly to elaborate the anti-anemic principle in a normal manner. There is considerable evidence that a defect of storage may exist. The intrinsic factor is probably not usually at fault. Achlorhydria is inconstant in these cases, and in one case [1] demonstration of the intrinsic factor in the stomach juice has been reported. Additional information of great interest has been obtained by a study of the content of anti-anemic principle in individual livers. By suitably preparing extracts of the liver of patients at autopsy, injecting them into patients with pernicious anemia, and observing the reticulocyte response, the presence or absence of the anti-anemic substance can be determined. This is regularly present in patients dying of unrelated diseases and in well treated cases of pernicious anemia in remission, but it is absent in untreated cases dying in an active stage of the disease. In some fatal cases of cirrhosis with macrocytic anemia, absence of the active principle in the liver has been demonstrated. Furthermore, parenteral injections of liver extract have relieved the anemia in some of the cases.

In one case of cirrhosis with anemia reported by Goldhamer et al. the liver did contain the anti-anemic principle. The anemia in this case was attributed to an inability of the liver to mobilize the substance normally. Furthermore, Wilkinson and Israels [3] have reported a small series of cases of macrocytic anemia of unknown etiology whose gastric juice contained free acid, who showed no evidence of gross liver disease, who were not benefited by injections of liver extract, and whose livers contained the anti-anemic principle. They assume here an inability of the hemopoietic tissues to utilize the active principle, even when it is present in the body in adequate quantities.

Such conclusions are based largely on the assumption that because the anemia is macrocytic, it must be related in some way to a disturbance in the production or utilization of the anti-anemic principle of liver. However, as Minot has pointed out, anemia with macrocytosis occurs occasionally in a variety of diseases (leukemia, aplastic anemia, hemolytic jaundice) in which there is no evidence that this substance is involved, and it is quite possible that the macrocytic anemia of liver disease also is unrelated to it. Injections of liver extract are ineffective in some cases. As yet there are no adequate studies of the bone marrow.

[3] Wilkinson, J. F., and Israels, M. C. G.: Achresthic anemia, Brit. Med. Jr., 1935, i, 139, 194.

That the liver may play some part in the elaboration of the active material as well as in its storage is suggested by the fact that the active material as extracted from liver differs significantly from that in the gastrointestinal tract (and in "ventriculin"). "Liver extract" is thermostable, it can be sterilized and is effective on parenteral injection. Its potency is increased by autolysis and by digestion with hog's stomach or normal gastric juice. The active material as it exists in the gastrointestinal tract cannot be extracted by the methods applicable to liver. It is destroyed by autolysis or prolonged digestion, it is thermolabile, and (except perhaps as "addisin") it has not been obtained in a potent form suitable for parenteral injection. There is, however, no direct proof that the liver is the site of this alteration, plausible as this appears. The change might occur in the intestinal mucosa during absorption. The fact that the material is stored in the liver does not prove that it is elaborated there. It is also abundant in kidney, and it is present in lesser concentration in other tissues (brain, placenta, etc.).

The study of these problems has been hampered by serious technical difficulties. The only available method (Castle's) for demonstrating the intrinsic factor is extremely cumbersome and quite impracticable except in large hospitals with an abundance of clinical material available. Demonstration of the active principle has been possible only by observing the response to it of untreated patients with pernicious anemia, who are now inconveniently rare. Hitherto the experimental production of the disease in animals has not been satisfactorily accomplished. Recent experimental work, however, offers hope that some of these difficulties may be eliminated. Thus Singer [4] has reported a reticulocyte response in rats following injection of gastric juice containing intrinsic factor, but negative responses with that from patients with pernicious anemia. Jacobson [5] obtained a definite reticulocyte response in selected normal guinea pigs following the administration of active principle, and he has used this as a means of detecting and measuring the amount of the active principle. While quantitatively the responses reported are not impressive, his work receives confirmation from the observations of Miller and Rhoads,[6] and it offers definite promise that animals will soon replace patients for this purpose.

Miller and Rhoads,[7] utilizing swine because the gastric juice of these animals contains intrinsic factor, have recently produced a disease condition closely resembling tropical sprue and (less closely) pernicious anemia by feeding a diet similar to that by means of which Goldberger produced black tongue in dogs. These animals showed a severe anemia (usually

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[5] Jacobson, B. M.: Response of guinea pig's reticulocytes to substances effective in pernicious anemia, Jr. Clin. Invest., 1935, xiv, 679.

[6] Miller, D. K., and Rhoads, C. P.: Reticulocyte response in guinea pigs following oral administration of certain anti-anemia substances, New England Med. Jr., 1935, ccxiii, 99.

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macrocytic), gastrointestinal disturbances with stomatitis, achlorhydria, loss of the intrinsic factor, disappearance of the active principle from the liver, and a hyperplastic megaloblastic bone marrow. The administration of liver extract caused a typical reticulocyte crisis, and clinical and hematological improvement. The possibilities for study which such experiments offer is obvious.

In summary, the only part played by the liver in erythropoiesis for which positive proof exists is that of a storehouse for the antianemic principle. The latter appears not to be an essential constituent of the liver cells. It is possible that the liver participates in the elaboration of the final product. It is also possible that a disturbance of its capacity to store or even to elaborate the active principle is responsible for the occasional development of macrocytic anemia in grave liver disease. That the liver may be found to exercise other important functions in the process of blood cell production is probable, but this is still pure speculation.

P. W. C.

BOOK REVIEWS

Radium Treatment of Skin Diseases, New Growths, Diseases of the Eyes and Tonsils. By FRANCIS H. WILLIAMS, M.D. 118 pages; 13 × 19 cm. Stratford Company, Boston. 1935. Price, $2.00.

This is a delightful and simply written little book of one hundred and eighteen pages divided into three sections. Part One consists of four chapters dealing with the nature and properties of radium and the use of radium in diseases of the skin and superficial new growths. Part Two includes seven chapters dealing with radium in diseases of the eyes, and Part Three is made up of five chapters dealing with the treatment of tonsils and lymphoid tissues in the throat. The twelve illustrations are simple and clear, although more illustrations could have been added to advantage.

One of the attractive features of this book is its author—a pioneer in the field of radium therapy, who began his work in 1900, when little was known about the biological effect of radium and its usefulness as a therapeutic agent. He was required to develop instruments to measure the penetration of tissues by the various rays in order to apply radium intelligently to clinical cases. This meant detailed careful experimentations. The book is a lasting record of Dr. Williams' fundamental discoveries and is of real practical value.

Parts Two and Three, dealing largely with clinical uses of radium in the specific fields covered by the book, are illustrated by typical cases, adding interest and clarity to the text. The sphere of clinical use, of course, is limited, but the book is concise and valuable for a ready reference text.

G. E. W.

Classical Contributions to Obstetrics and Gynecology. By HERBERT THOMS, M.D., Associate Professor of Obstetrics and Gynecology, Yale University, and HOWARD A. KELLY, M.D. 265 pages; 15 × 23.5 cm. Charles C. Thomas, Springfield, Illinois. 1935. Price, $4.00.

In this book the author tells about the great specialists in women's diseases, beginning with Soranus of Ephesus who lived in the Second Century. The contributions of any gynecologists or obstetricians now living have been omitted as has all material published since 1900. There has been no attempt to make this volume encyclopedial in type but rather the author has exercised the right of personal choice in selecting those men to write about who in his opinion have made the most important contributions to the development of gynecology and obstetrics.

The general practitioner, as well as the specialist, will be glad to become better acquainted with the great obstetricians, who lived in the Eighteenth Century, among whom might be mentioned Mauriceau and Smellie but probably the most interesting part of the book is that which deals with the accomplishments of Charles White, Oliver Wendell Holmes, Semmelweiss and Pasteur, all of whom lived in the Nineteenth Century. It is to these men that the human race should be always grateful for giving the medical profession a clearer understanding of puerperal infection.

The last part of the book tells of the lives and achievements of those pioneers in pelvic surgery, who lived in the last Century, among whom we Americans are proud to claim as our own—Ephraim McDowell, Nathan Smith, Marion Sims and many others.

Dr. Thoms work should be of special interest to those who instruct medical students in obstetrics and diseases of women. A little medical history interspersed through a lecture or clinic often adds interest, and the students through learning what

their forebears have accomplished in the struggle against disease may be stimulated to "carry on the torch." L. B.

Gynecological and Obstetrical Tuberculosis. By Dr. Edwin M. Jameson, B.S., Fellow of Trudeau Foundation, Attending Surgeon, Saranac Lake General Hospital and Reception Hospital. 256 pages. Lea and Febiger, Philadelphia. 1935. Price, $3.50.

This monograph coming from the Trudeau Foundation should be of great interest not only to the gynecologist and obstetrician but also to the whole medical profession. The book is divided into three parts. The first deals with the alterations in the physiology of the female genital apparatus brought about by pulmonary tuberculosis. The second covers the various forms of female genital tuberculosis, while the third or last part of the book is given over to a discussion of the problem of pregnancy in the tuberculous woman.

The author has thoroughly reviewed the literature and there is a 36 page bibliography. However, what makes this monograph of such distinct value are the conclusions that Dr. Jameson himself has reached, based on his own studies of the tremendous amount of clinical material available in the Trudeau Clinic. This is, indeed, a book well worth having.

L. B.

Pediatric Treatment. By Philip S. Potter, M.D. 578 pages; 16 × 24 cm. Macmillan Co., New York. 1935. Price, $5.00.

The organization of material is excellent. Following the necessary basic review of general, local and emergency treatment, plus a chapter on pharmaceutics; the diseases according to systems are then presented by a brief résumé of clinical symptoms and signs with the therapeutic indications, followed by the therapeusis proper, under the subdivisions of general and symptomatic measures. Whenever prophylactic or quarantine measures are requisite they are described in the appropriate subdivision. Prescriptions are amply supplied, and a final chapter consisting entirely of prescriptions of outstanding pediatricians is presented. The book is most complete; nearly every possible subject regardless of the value of treatment has been devoted space.

A therapeutic text almost uniformly reflects the climatological location of the author and likewise methods that are common usage in his (the author's) location. To the preceding, Dr. Potter of California, is no exception, as may be evidenced by the statement on Page 220 (Treatment of Anorexia), "the child should be held upright after feeding and then taken out in the sunshine for an hour."

The author is a firm advocate of purging, even in many cases in which it would seem that this measure was of questionable value. The inclusion of practices in vogue elsewhere would have been a helpful addition to this volume.

The treatise is easily read. There is an excellent bibliography. It contains much of interest but cannot be said to constitute an advance over more familiar texts.

E. B.

Mouth Infection. By Oliver T. Osborne, M.D. 119 pages; 14 × 21 cm. 1934. Price, $2.00.

This book is an interesting treatise on the importance of mouth infection, its relationship to disease and the necessity for coöperation between physician and dentist in treatment. According to the author, many diseases, such as boils, neuritis, stomach and intestinal ulcers, endocrine disturbances, endocarditis, etc. are often caused by oral infections.

In discussing devitalized or pulpless teeth, the author states that even when teeth are negative to roentgenographic examination, upon removal the *Streptococcus viridans* may be found within the root canal.

Many case histories are included which are classed in several groups. With each history, there is a report of the oral examination. The reports of reëxamination following medical and dental treatment reveal many interesting reactions.

The relationship of infected tonsils to systemic disorders is discussed and supplemented with actual case histories showing reactions following their removal.

Vincent's infection, its dangers and treatment are described.

The book closes with a discussion as to the possibility of the tooth brush, which is in general use today, causing continued reinfection of the mouth by being improperly kept.

The author's point of view is often stimulating even though his conclusions may not be fully supported.

B. M. D.

PROGRAM

TWENTIETH ANNUAL SESSION
AMERICAN COLLEGE OF PHYSICIANS
DETROIT, MICHIGAN

March 2–6, 1936

GENERAL SESSIONS

James Alex. Miller, President

DETROIT COMMITTEES

Charles G. Jennings,* General Chairman

COMMITTEE ON ARRANGEMENTS

C. G. Jennings,* Chairman — J. D. Bruce (Ann Arbor), Vice-Chairman

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Thaddeus Walker — R. C. Jamieson
R. H. Stevens — W. J. Stapleton
F. G. Buesser — W. A. Evans

Mrs. F. W. Hartman

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C. C. Sturgis, University Hospital, Ann Arbor
H. A. Freund, Harper Hospital
J. T. Watkins, Grace Hospital
F. J. Sladen, Henry Ford Hospital
B. H. Douglas, Herman Kiefer Hospital
T. B. Cooley, Children's Hospital
Douglas Donald, Receiving Hospital

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R. A. C. Wollenberg

COMMITTEE ON AUDITORIUM

R. H. Stevens, Chairman

Lawrence Reynolds — F. R. Menagh
H. A. Luce — N. J. Whalen
R. L. Fisher — W. H. Gordon

W. J. Wilson

* Deceased Jan. 9, 1936.

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COMMITTEE ON ENTERTAINMENT OF VISITING WOMEN

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Mrs. H. W. Plaggemeyer
Mrs. R. C. Jamieson
Mrs. Wm. J. Stapleton
Mrs. Hugh Stalker
Mrs. James D. Bruce
Mrs. C. C. Sturgis

INVITATION

Detroit, one of the oldest of the large cities of the country and, in a sense, one of the newest, joins with Ann Arbor, the home of Michigan's great University, in extending for the second time a cordial invitation to the American College of Physicians to hold in these cities the Twentieth Annual Session of the College.

The Michigan State Medical Society, the Wayne County Medical Society, the Detroit Academy of Medicine; the Medical Departments of the University of Michigan and Wayne University have, through their officers, assured the College of their hearty coöperation with the local committee to make the Session a success. The Department of Health and the Welfare Department with the wealth of clinical material under their control will give us their unqualified support.

The seven hospitals, at which will be given the clinical and demonstration programs, have a total bed capacity of 4051. The clinical amphitheaters and assembly rooms of these hospitals will accommodate 2000 persons.

Many distinguished clinicians from other cities of the United States and Canada will aid the local physicians, and this will give to the clinical program a truly cosmopolitan character.

The day in Ann Arbor will give to members the opportunity to visit the University of Michigan and to have a close-up view of the activities of its teaching hospital and laboratories.

The features of historic interest of older Detroit have been largely overgrown during the present century by its rapid rise to the position of the fourth city of the country in population and by the change in its character from a gracefully growing community to the greatest industrial city of the world.

While Detroit cannot rival the old cities of the East in structures and objects

GENERAL INFORMATION

HEADQUARTERS

BOOK-CADILLAC HOTEL
Washington Blvd.

The Book-Cadillac Hotel will be not only the headquarters hotel for Officers, Regents, and Governors of the College, and so far as facilities permit, for members and guests, but also the general headquarters for registration, technical exhibits and all general scientific sessions.

LIST OF DETROIT HOTELS

	No. of Rooms	Blocks Removed From Head-quarters	RATES PER DAY				
			Room—One Person		Room—Two Persons		
			With Bath	Without Bath	With Bath	Without Bath	Suites
Book-Cadillac, Washington Blvd.	1200		$3.00–5.00		$4.50–8.00		$10.00–20.00
Briggs, 114 W. Adams	200	5	2.00 up		3.00 up		
Detroiter, Woodward & Adelaide	750	7	2.00 up	1.50 up	3.00 up	2.50 up	
Detroit Leland, Cass at Bagley	800	3	2.50 up		3.50 up		
Fort Shelby, Lafayette at First	900	3	2.00 up	1.50 up	3.00 up		
Madison Lenox, Madison & John R.	300	5	2.00 up	1.25 up	2.50 up	2.00 up	
Norton, Jefferson & Griswold	250	5	1.50 up	1.25 up	2.50 up	2.00 up	
Statler, Grand Circus Park	1000	3	2.50 up		4.50 up		
Tuller, Park & Adams	800	3	2.00 up		3.50 up		
Wolverine, Witherell at Elizabeth	500	6	2.00 up		3.00 up		

of national historic interest, it can entertain its guests with the marvels of modern industrialism. It is the world's center of automobile production. Ninety per cent of the passenger car output of the country is made in the city and its environs. A visit to one of the great factories is an education in the methods of quantity production.

Belle Isle Park is one of the beauty spots of the city. Among the outstanding objects of interest are the Art Museum and Public Library at the Art Center, the unique American Museum at Greenfield Village at Dearborn and the Cranbrook School at Bloomfield Hills.

Since the Session of 1926 the hospitals of Detroit have doubled their capacity with modern buildings and equipment, and brought their laboratories and research departments to a high state of efficiency.

It is the hope of the local committees that their efforts will make the coming Session memorable for its educational value and for its enjoyable entertainment.

DIRECTORY

Headquarters	Book-Cadillac Hotel
Registration	Fourth Floor, Book-Cadillac Hotel
Technical Exhibits	Fourth Floor, Book-Cadillac Hotel
General Scientific Sessions	Ballroom, Book-Cadillac Hotel
Convocation	Ballroom, Book-Cadillac Hotel
Annual Banquet	Ballroom, Book-Cadillac Hotel

WHO MAY REGISTER—

(*a*) All members of the American College of Physicians in good standing for 1936 (dues, if not paid previously, may be paid at the Registration Bureau).

(*b*) All newly elected members.

(*c*) Members of the Wayne and Washtenaw Counties Medical Societies, without registration fee, upon presentation of their 1936 membership cards.

(*d*) Medical students pursuing courses at the Wayne University, College of Medicine, and the University of Michigan Medical School, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions; exhibits and general sessions.

(*e*) House Officers of the hospitals participating in the program, upon presentation of proper identification; exhibits and general sessions.

(*f*) Members of the Medical Corps of Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.

(*g*) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of $12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU.—Temporary Registration Bureau will be open at the Book-Cadillac Hotel on Sunday afternoon and evening, March 1. The permanent Registration Bureau will be located on the fourth floor of the Book-Cadillac Hotel. Hours: 8:30 a.m. to 6:00 p.m., daily, March 2 to 6.

REGISTRATION BLANKS FOR ALL CLINICS AND DEMONSTRATIONS will be sent with the formal program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

THE CASHIER'S DESK at the Registration Bureau will receive payment of dues still delinquent, and accept orders for Banquet tickets, the College Key, the framed Fellowship Pledge, the Fellowship Certificate Frame and subscriptions to the ANNALS OF INTERNAL MEDICINE.

BULLETIN BOARD FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau at the Book-Cadillac Hotel.

TRANSPORTATION.—Round trip tickets may be procured on the basis of one and one-third of the current one-way first class fares, with minimum excursion fare of $1.00 for the round trip, upon presentation of identification certificates to be procured from the Executive Secretary of the American College of Physicians. The reduced fares apply for physicians and dependent members of their families.

Members are privileged to make the going journey by one route and return by another route. The fare for children of five and under twelve years of age will be one-half of the round trip fare for adults; children under five years of age free when accompanied by parents or guardian. Stop-overs will be allowed at all stations within final limit on either going or return trip, or both, upon application to conductors.

Before purchasing tickets, members must secure from the Executive Secretary an Identification Certificate, to entitle them to the reduced fares.

In general, tickets will be sold from February 19 to March 4, depending upon the relative distance from Detroit, with a return limit of thirty days in addition to date of sale.

All tickets must be validated by a special railroad agent at the Detroit Headquarters at the Book-Cadillac Hotel from March 2 to 6.

LOCAL TRANSPORTATION.—Transportation to the University Hospital, Ann Arbor, on Wednesday, March 4, will be by buses. Fare for the round trip will be $1.80. Tickets should be purchased at the desk near the Registration Bureau before 8:00 o'clock, Tuesday evening, in order that a sufficient number of buses will be available.

Buses will be stationed at the Book-Cadillac Hotel at 8:00 o'clock, Wednesday morning, and will start for Ann Arbor as rapidly as filled. Running time—1 hr., 20 min.

Street cars of the Hamilton Avenue line pass the Henry Ford and the Herman Kiefer Hospitals. These cars cross Washington Boulevard at Grand River Avenue, two blocks north of the Book-Cadillac Hotel. The Woodward Avenue cars going north pass within two blocks of Harper, The Grace and The Children's Hospitals.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 5:30 p.m., Thursday, March 5, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary, and the induction to office of the new President, Dr. Ernest B. Bradley, Lexington, Kentucky.

BOARD AND COMMITTEE MEETINGS.—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

A *special dinner* will be tendered *to the Board of Governors* by members of the Board of Regents at the Book-Cadillac Hotel, Sunday evening, March 1. An announcement of the time and place will be made later. Members of the Board of Governors are cordially invited.

COMMITTEE ON CREDENTIALS

Sunday, March 1, 10:00 a.m.....Parlor C, Fourth Floor, Book-Cadillac Hotel

BOARD OF REGENTS

Parlor C, Fourth Floor, Book-Cadillac Hotel

Sunday, March 1, 2:00 p.m.
Tuesday, March 3, 12:00 m.*
Friday, March 6, 12:00 m.*

BOARD OF GOVERNORS

Parlor C, Fourth Floor, Book-Cadillac Hotel

Monday, March 2, 5:00 p.m.
Wednesday, March 4, 12:00 m.*
* *Buffet luncheon served.*

SPECIAL FEATURES

MONDAY, MARCH 2, 1936

THE ANNUAL SMOKER will be given immediately following the scientific program, about 10:20 o'clock in the evening, in the Grand Ballroom of the Book-Cadillac Hotel. An unusual program of music and other entertainment will be given. Ladies are invited.

WEDNESDAY, MARCH 4, 1936

CONVOCATION OF THE COLLEGE.—8:15 p.m., Ballroom, Book-Cadillac Hotel. All Masters and Fellows of the College and those to be received in Fellowship should be present. Newly elected Fellows who have not yet been received in Fellowship are requested to assemble in the Reception Room to the rear of the Grand Ballroom of the Book-Cadillac Hotel at 7:30 o'clock, preparatory to the formation of the procession. They will occupy especially reserved seats in the central section of the Ballroom, to which they will be conducted by the Convocation marshall promptly at 8:15. As this is the most formal meeting of the College, it is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

Following the Convocation Ceremony, the President will present the John Phillips Memorial Medal for 1935–36. Thereafter will follow the Convocational Oration, "The Rôle of Emotion in Disease," by Dr. Walter B. Cannon, Professor of Physiology, Harvard University Medical School, Boston.

The President, Dr. James Alex. Miller, of New York City, will then deliver the annual presidential address, "The Changing Order in Medicine," to the Masters, Fellows and Associates of the College.

The Presidential Reception, in the Reception Room to the rear of the Grand Ballroom, will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception. All members and guests are invited to remain for dancing in the Grand Ballroom following the Reception.

THURSDAY, MARCH 5, 1936

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Grand Ballroom of the Book-Cadillac Hotel at 8:00 p.m. All members of the College, physicians of Detroit and Ann Arbor and visitors attending the Session, with their families, are cordially invited to attend. Consult the banquet program to be printed later for announcement of the toastmaster and speakers.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The headquarters of the visiting ladies will be in the Founders Room on the fifth floor of the Book-Cadillac Hotel, near the Grand Ballroom.

The program for their entertainment has been arranged to give ample time for sightseeing, shopping and recreation. A folder giving points of interest, shops, theaters, concerts, etc., will be issued by the local committee.

ART CENTER.—The Detroit Public Library and the Detroit Institute of Art, Woodward Avenue between Farnsworth and Kirby Streets. The Public Library contains the celebrated murals of Gari Melchers, and the Art Institute the much discussed murals of Diego Rivera.

THE WAYNE COUNTY MEDICAL SOCIETY BUILDING, 4421 Woodward Avenue. This is the meeting place of the medical men of the city and county. Its club features make it very popular both to members of the Society and the Women's Auxiliary, which has a large and active membership. An excellent restaurant serves luncheon and dinner at moderate prices.

Members of the College are cordially invited to visit the Society's home and inspect its work in the field of medical economics.

ANN ARBOR

LIBRARIES OF THE UNIVERSITY OF MICHIGAN contain about one million volumes, and include many notable collections: 6000 listed items of Greco-Egyptian papyri, in size and importance surpassed only by the collections in London, Berlin and Cairo; a collection of Persian and Arabic manuscripts once owned by the Sultan Abdul Hamid; the Macmillan Shakespeare Library, 6525 volumes; the Parsons Library of Political Science, 6076 volumes; the Goethe Library, 1131 volumes; the William L. Clements Library of American History with its collection of books, manuscripts, maps and newspapers relating to early American history.

THE LAW QUADRANGLE will be found of especial interest. It consists of the Lawyers' Club, the dormitories attached to the Club, the Legal Research building, and the Law School building, Hutchins Hall.

THE MUSEUMS BUILDING houses the zoölogical, anthropological, and paleontological collections of the University, including a number of important special collections, such as the Stevens Oriental Collection and the Chinese Government Exhibit from the New Orleans Exposition.

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the fourth floor of the Book-Cadillac Hotel, on the way to registration and General Sessions.

Because of limitation of room and the impossibility of expanding the number of booths, many firms were unable to obtain space. Many of these firms have exhibited before the College previously, have established contacts among our members and would be in the exhibit again this year if possible. Among them are the following: The Doak Company, Cleveland; Kellogg Company, Battle Creek; Gradwohl School of Laboratory Technique, St. Louis; The Burdick Corporation, Milton, Wis.; Aznoe's National Physicians' Exchange, Chicago; Ayerst, McKenna & Harrison, Ltd., Montreal; The Battle Creek Food Company, Battle Creek; Ciba Company, New York; Spicer and Company, Glendale; Ernst Bischoff Company, Inc., New York; S. H. Camp & Company, Jackson; Westinghouse X-Ray Company, Inc., Long Island City; Austin, Nichols & Co., Inc., "Vichy Celestins," Brooklyn.

However, the exhibit will be very representative, and will include medical literature and texts, pharmaceutical products, apparatus and appliances, and many other items of special interest to physicians, especially internists. These exhibits will afford an opportunity for physicians to keep informed of the latest literature and the newest products in the field of medicine generally; the educational value of these exhibits should not be overlooked. Furthermore, the exhibitors contribute much not only to the interest of the meeting, but to the financial support of these scientific sessions. Every physician is urged to visit each of the booths, for he will certainly find something new, interesting and scientifically valuable. The exhibits will be closed on Wednesday, Ann Arbor Day. Special intermissions in the general program will be arranged, providing additional time for the inspection of exhibits.

TECHNICAL EXHIBITORS

American College of Physicians

Detroit, March 2–6, 1936

	Space
American Hospital Supply Corporation, Chicago, Ill.	20
Appleton-Century Company, D., New York, N. Y.	55
Arlington Chemical Company, The, Yonkers, N. Y.	16
Bausch & Lomb Optical Co., Rochester, N. Y.	9
Becton, Dickinson & Co., Rutherford, N. J.	10
Bilhuber-Knoll Corporation, Jersey City, N. J.	31–32
Burroughs Wellcome & Co. (U. S. A.), Inc., New York, N. Y.	34–35
Cambridge Instrument Co., New York, N. Y.	28
Cameron's Surgical Specialty Co., Chicago, Ill.	15
Collins, Inc., Warren E., Boston, Mass.	25
Davies, Rose & Co., Ltd., Boston, Mass.	40–41
Davis Company, F. A., Philadelphia, Pa.	53
Fischer & Co., H. G., Chicago, Ill.	50–51
Fougera and Co., Inc., E., New York, N. Y.	21
General Electric X-Ray Corporation, Chicago, Ill.	57–58–59
Gerber Products Co., Fremont, Mich.	52
Lea & Febiger, Philadelphia, Pa.	46
Lederle Laboratories, Inc., New York, N. Y.	29
Lippincott Company, J. B., Philadelphia, Pa.	27
M & R Dietetic Laboratories, Inc., Columbus, Ohio	8
Macmillan Co., The, New York, N. Y.	63
Maltine Company, The, New York, N. Y.	14
Mead Johnson & Company, Evansville, Ind.	17–18
Medical Bureau, The, Chicago, Ill.	47
Merck & Co., Inc., Rahway, N. J.	43–44–45
Merrell Company, The Wm. S., Cincinnati, Ohio	54
Middlewest Instrument Company, Chicago, Ill.	22
Morris & Co. Ltd., Inc., Philip, New York, N. Y.	A
Mosby Company, The C. V., St. Louis, Mo.	19
Oxford University Press, New York, N. Y.	62
Parke, Davis & Company, Detroit, Mich.	1–2–3–4–5
Patch Company, The E. L., Boston, Mass.	23–24
Petrolagar Laboratories, Inc., Chicago, Ill.	11
Ralston Purina Company, St. Louis, Mo.	33
Rare Chemicals, Inc., Nepera Park, N. Y.	36–37
Sanborn Company, Cambridge, Mass.	49
Sandoz Chemical Works, Inc., New York, N. Y.	30
Saunders Company, W. B., Philadelphia, Pa.	48
Schering Corporation, Bloomfield, N. J.	26
Smith, Kline & French Laboratories, Philadelphia, Pa.	6–7
Squibb & Sons, E. R., New York, N. Y.	42
Taylor Instrument Companies, Rochester, N. Y.	12–13
Winthrop Chemical Company, Inc., New York, N. Y.	38–39
Wyeth & Brother, Inc., John, Philadelphia, Pa.	60–61

GENERAL SESSIONS

In arranging the program for the General Sessions this year, an effort has been made to present a summary of the progress of medical knowledge in a few selected fields, and in carrying out this plan we are very fortunate to have secured the co-operation of outstanding leaders in various branches of medicine.

This review plan of presentation will be followed in the consideration of the following diseases:

Cardiac Disease, Diabetes, Virus Diseases, including *Common Colds, Silicosis, Arthritis,* and also the treatment of *Pneumonia,* of *Pulmonary Tuberculosis* and of *Syphilis.*

In addition, the program contains special contributions to other phases of medicine:

OUTLINE OF SESSION

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	March 2	March 3	March 4	March 5	March 6
9:00 a.m. to 12:00 m.	Morning free. Registration, Exhibits, etc.	1st Clinical Session	"ANN ARBOR DAY" 2nd Clinical Session (beginning at 10:00)	3rd Clinical Session	4th Clinical Session
12:00 m. to 2:00 p.m.	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
2:00 p.m. to 5:30 p.m.	**1st General Session**	**3rd General Session**	**5th General Session** (finishing at 4:05)	**6th General Session** Annual Business Meeting	**7th General Session**
5:30 p.m. to 8:00 p.m.	Dinner	Dinner	Dinner		Dinner
8:00 p.m. to 10:00 p.m.	**2nd General Session** followed by Smoker	**4th General Session**	Convocation, followed by President's Reception and Dance	ANNUAL BANQUET	

Medical History.—It has been thought desirable to include one paper upon this cultural subject as distinct from the purely clinical aspects of medicine.

Neurology.—The subject of the neuroses is considered from the standpoint of their causation and also of their treatment, and a very recent procedure of great value in the diagnosis and location of brain tumors will be described.

Vascular Disturbances will be discussed from the standpoints of physiology and of hemodynamics.

Diseases of Children.—The subject of the use of convalescent serum in the treatment of acute infectious diseases, and also the treatment of the sequelae of birth injuries will be presented with the aid of motion pictures.

Endocrinology.—Some of the problems connected with the internal secretions, in addition to those of diabetes, will be discussed.

Preventive Medicine and Public Health.—In the presentation and discussion of both syphilis and silicosis, the preventive and public health aspects of these diseases will be emphasized.

Medico-Dental Problems will be discussed both from the standpoint of medicine and of dentistry.

The *Organs of Digestion* are considered in the discussion of certain conditions of the liver and of the intestines, including the treatment of constipation.

Respiratory Diseases.—In addition to the reviews of the treatment of pneumonia and of pulmonary tuberculosis, special phases of respiratory diseases, both tuberculous and non-tuberculous, will be presented.

Experimental Studies of the Revived Human Heart will be presented in a fascinating manner by means of a motion picture.

Ann Arbor Session.—An unusual and unique feature of our program is the assignment of one entire day to the medical staff of the University of Michigan at Ann Arbor. The program for that day is very varied and promises to be of exceptional interest.

The *Convocational Oration* will be delivered by Dr. Walter B. Cannon, Professor of Physiology at the Harvard University Medical School. This address will present a physiological approach to some of the important problems of medicine, under the title, "The Rôle of Emotion in Disease." Professor Cannon's reputation as a scientist and public speaker assures us of a most instructive and enjoyable evening. This address, as well as that of the President of the College, which will be delivered on the same evening, will contain much of general as well as of medical interest, so that it is hoped that many of our lay guests will find it both interesting and enjoyable to attend this session.

GENERAL SESSIONS

Ballroom, Book-Cadillac Hotel, Detroit, Mich.

FIRST GENERAL SESSION

Monday afternoon, March 2, 1936

p.m.

2:00 Addresses of Welcome:

CHARLES G. JENNINGS, General Chairman of the Twentieth Annual Session.

GROVER C. PENBERTHY, President, Michigan State Medical Society.

ROBERT C. JAMIESON, President, Wayne County Medical Society.

HENRY F. VAUGHAN, Commissioner of Health, City of Detroit.

Response to Addresses of Welcome:

JAMES ALEXANDER MILLER, President of the American College of Physicians.

2:30 The History of Hospitals, with Special Reference to Some of the World's Oldest Institutions.
HENRY R. CARSTENS, Detroit, Mich.
3:00 Viruses and the Diseases Caused by Them.
THOMAS M. RIVERS, New York, N. Y.
3:30 INTERMISSION.
4:15 Recent Advances in the Study of Common Cold and Influenza.
A. R. DOCHEZ, New York, N. Y.
4:45 Treatment of Birth Injuries and Allied Problems. (Illustrated with Motion Picture.)
EARL R. CARLSON, New York, N. Y.
5:05 The Localization and Diagnosis of Tumors of the Brain by Olfactory Tests.
CHARLES A. ELSBERG, New York, N. Y.
5:35 ADJOURNMENT.

SECOND GENERAL SESSION

Monday Evening, March 2, 1936

Presiding Officer

JAMES E. PAULLIN, Atlanta, Ga.

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p.m.
8:00 Diabetes Today and Tomorrow.
ELLIOTT P. JOSLIN, Boston, Mass.
8:30 Disturbances of the Endocrine Balance and Their Relation to Diseases of Metabolism.
C. N. H. LONG, Philadelphia, Pa.
9:00 Ulcerative Conditions of the Small Intestine.
PHILIP W. BROWN and J. DEJ. PEMBERTON, Rochester, Minn.
9:20 Use of Foods in the Treatment of Constipation.
WILLIAM H. OLMSTED, St. Louis, Mo.
9:40 Chronic Arthritis—A General Disease Requiring Individualized Treatment.
ERNEST E. IRONS, Chicago, Ill.
10:00 ADJOURNMENT.

10:20 o'Clock

SMOKER

Ballroom, Book-Cadillac Hotel

An unusual program of music and other entertainment has been arranged. Ladies are invited.

Admission by registration badge.

THIRD GENERAL SESSION

Tuesday Afternoon, March 3, 1936

Presiding Officer

ERNEST B. BRADLEY, Lexington, Ky.

p.m.

2:00 Errors in the Interpretation of Cardiovascular Symptoms and Signs.
PAUL D. WHITE, Boston, Mass.

2:30 Errors in the Clinical Application of Electrocardiography.
WILLIAM B. BREED, Boston, Mass.

2:55 Errors in Cardiovascular Roentgen-Ray Interpretation.
HUGO ROESLER, Philadelphia, Pa.

3:20 A Survey of the Newer Methods of Cardiac Therapy.
WILLIAM D. STROUD, Philadelphia, Pa.

3:45 INTERMISSION.

4:25 Studies of the Revived Human Heart. (Motion Picture.)
WILLIAM B. KOUNTZ, St. Louis, Mo.

4:45 Some Factors in the Etiology of the Psychoneuroses.
LOUIS CASAMAJOR, New York, N. Y.

5:15 The Treatment of Psychoneuroses.
AUSTEN FOX RIGGS and HORACE K. RICHARDSON, Stockbridge, Mass.

5:45 ADJOURNMENT.

FOURTH GENERAL SESSION

Tuesday Evening, March 3, 1936

Presiding Officer

WILLIAM J. KERR, San Francisco, Calif.

p.m.

8:00 The Public Health Control of Syphilis.
THOMAS J. PARRAN, JR., Albany, N. Y.

8:30 Modern Treatment Methods of Early Syphilis.
JOSEPH EARLE MOORE, Baltimore, Md.

9:00 The Prophylactic and Therapeutic Value of Convalescent Sera in Some of the Acute Infectious Diseases.
WILLIAM THALHIMER, New York, N. Y.

9:20 Medico-Dental Relations: A Dentist's Viewpoint.
J. T. O'ROURKE, Louisville, Ky.

9:40 The Interrelations of Dentistry and Internal Medicine.
SYDNEY R. MILLER, Baltimore, Md.

10:00 ADJOURNMENT.

ANN ARBOR SESSION

Wednesday, March 4, 1936

The entire program, exclusive of the Convocation in the evening, will be conducted at the University of Michigan, Ann Arbor.

FIFTH GENERAL SESSION

Wednesday Afternoon, March 4, 1936

Conducted by the Staff of the Department of Medicine of the University of Michigan.

Ballroom of the University of Michigan Union.

Presiding Officer

JAMES D. BRUCE, Ann Arbor, Mich.

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p.m.

2:00 Address of Welcome.
ALEXANDER G. RUTHVEN, President of the University of Michigan.

2:10 The Medical and Economic Advantages of an X-Ray Chest Survey of All Hospital Admissions.
FRED J. HODGES.

2:35 Clinical Aspects of Water Balance and Dehydration.
FREDERICK A. COLLER.

3:00 The Relation between Emotion and Disturbance of Physiologic Function.
CARL D. CAMP.

3:25 The Present Status of Pernicious Anemia; Experience with 600 Cases over Eight Years.
CYRUS C. STURGIS.

3:50 The Surgical Treatment of Hypertension.
MAX M. PEET.

4:05 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, March 4, 1936

8:15 o'Clock

Ballroom, Book-Cadillac Hotel

The general profession and the general public are cordially invited. No special admission tickets will be required.

1. Convocation Ceremony.
2. Presentation of the John Phillips Memorial Medal.
3. Convocational Oration: "The Rôle of Emotion in Disease."
WALTER B. CANNON, Professor of Physiology, Harvard University Medical School, Boston, Mass.

4. Presidential Address: "The Changing Order in Medicine."
JAMES ALEXANDER MILLER, New York, N. Y.

President's Reception

Reception Room, Ballroom, Book-Cadillac Hotel

The Reception will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

Dancing

SIXTH GENERAL SESSION

Thursday Afternoon, March 5, 1936

Presiding Officer

JAMES B. HERRICK, Chicago, Ill.

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p.m.

2:00 Clinical Manifestations and Studies in Parenchymatous Hepatitis.
HUGO A. FREUND, Detroit, Mich.

2:20 Treatment of Pneumonia.
RUFUS I. COLE, New York, N. Y.

2:50 Adolescent Disturbances of Endocrine Function, the Importance of Their Recognition and Treatment.
CHARLES H. LAWRENCE, Boston, Mass.

3:20 Vascular Physiology and Clinical Medicine.
EUGENE M. LANDIS, Philadelphia, Pa.

3:45 INTERMISSION.

4:30 The Diagnosis of Silicosis with Special Reference to Roentgenologic Manifestations.
LEROY U. GARDNER, Saranac Lake, N. Y.

4:50 Silicosis from the Public Health and Economic Viewpoint.
A. J. LANZA, New York, N. Y.

5:10 Some Combinations of Certain Tuberculous and Non-Tuberculous Pulmonary Lesions.
F. MAURICE MCPHEDRAN, Philadelphia, Pa.

5:30 ADJOURNMENT.

The *Annual General Business Meeting* of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Official reports from the Executive Secretary and Treasurer will be read; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. Ernest B. Bradley, will be inducted into office.

Thursday Evening, 8:00 o'Clock

Ballroom, Book-Cadillac Hotel

THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

SEVENTH GENERAL SESSION

Friday Afternoon, March 6, 1936

Presiding Officer

GEORGE MORRIS PIERSOL, Philadelphia, Pa.

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p.m.

2:00 Tuberculosis among Student Nurses; a Five-Year Study at Bellevue Hospital.
J. BURNS AMBERSON, JR., and H. MCLEOD RIGGINS, New York, N. Y.

2:20 The Present Status of the Treatment of Pulmonary Tuberculosis.
LAWRASON BROWN, Saranac Lake, N. Y.

2:50 Postural Pulmonary Emphysema.
WILLIAM J. KERR, and JOHN B. LAGEN, San Francisco, Calif.

3:10 Clinical Problems of Hemodynamics in Nephritis and High Blood Pressure.
ARTHUR R. ELLIOTT, Chicago, Ill.

3:30 INTERMISSION.

4:15 The Lethal Effect of Solar Radiation on Guinea Pigs.
MAX PINNER and AARON E. MARGULIS, Oneonta, N. Y.

4:25 Acute Syphilitic Myocarditis—Simulating Myocardial Infarction; With a Case Report.
EDWARD C. REIFENSTEIN, Syracuse, N. Y.

4:45 ADJOURNMENT.

THE CLINIC SESSIONS

The program of the Clinic Sessions—from 9:00 a.m. to noon at Detroit (10:00 a.m. to noon at Ann Arbor)—has been modelled on those which have proved so successful in recent years. Emphasis has been placed on clinics in the true sense of the word, and there is scarcely a field of medicine which is not fully represented on the program. In addition to the various aspects of internal medicine, there are ample offerings in the subjects of pediatrics, psychiatry, neurology, roentgenology as well as in certain more distant fields which are still of importance to the internist, as for example bronchoscopy and certain surgical subjects. Ample opportunities in ward walks are offered for those who wish to see patients at close range and hospital methods in Detroit and Ann Arbor. Scientific demonstrations are offered on some programs that the visitors may see the research work actually being carried on at this time in the various laboratories.

The clinic program offers daily a capacity of over 2,000, scattered over six hospitals in Detroit and one in Ann Arbor. These hospitals are the following:

A. Harper Hospital was opened for the care of patients on January 1, 1866. It has grown steadily until now it has a capacity of 625 beds caring for medical, surgical and obstetrical patients. Last year 13,478 patients received 117,376 days' hospitalization. It has well equipped pathological and x-ray departments and a large Outpatient Department Clinic with an average daily attendance of 294.

B. The Receiving Hospital is a city institution under the supervision of the Department of Public Welfare. It was opened in 1915 for the care of needy general hospital cases and the temporary detention of mental patients. In 1921 and again in 1927 notable additions were made to the hospital building. It now has a capacity of 650 beds.

C. The Henry Ford Hospital was incorporated under the laws of the State of Michigan on October 15, 1915. It is a general hospital with a bed capacity of 608, offering services to both in-patients and out-patients in all branches of medicine, surgery, pediatrics and obstetrics. In 1925 a school of nursing and hygiene was opened and operates in conjunction with the hospital.

D. The Grace Hospital was founded in 1888 by a group of public spirited citizens. In 1889 a Training School for Nurses was organized. A large Memorial Unit erected in 1931 increased the capacity to 529 beds. The hospital is a non-profit institution governed by an independent Board of Trustees. It cares for all forms of disease, except contagious and insane.

E. The Herman Kiefer Hospital, owned by the City of Detroit, controlled by the Board of Health. It has a capacity of 1,400 beds—services for all stages of tuberculosis in any form, contagious diseases, and maternity cases. A teaching hospital affiliated with the Wayne University, College of Medicine; houses the Department of Health Laboratories and the department's Outpatient Tuberculosis Clinics.

F. Children's Hospital of Michigan. The Children's Free Hospital Association was founded in 1886 by a group of Detroit women. In 1922 it was merged with the Michigan Hospital School, an organization for the care of crippled children, to form the Children's Hospital of Michigan. The city hospital with a capacity of 239 beds is for the care of acute medical and surgical patients. The hospital school, capacity 240 beds, is located in the country and is used as a convalescent home.

G. The Hospital of the University of Michigan opened in 1925 with a capacity of 825 beds, to increase the facilities of the old University Hospital which was built in 1869 and served as a teaching hospital for 56 years. There are now a total of 1,312 beds available for the care of the sick and for teaching, as well as ample provision for research.

The detailed programs at each of these hospitals are not printed herein. At the time this copy goes to press, it is too far in advance to name the actual cases that will be presented and to give the detailed titles of clinics and demonstrations. Furthermore, the full program of clinics and demonstrations would occupy too great space in this issue of the ANNALS. The official program, complete in all respects, will soon be distributed from the Executive Offices of the College.

COLLEGE NEWS NOTES

Nominations for Elective Officers

The Committee on Nominations of The American College of Physicians, in accordance with the provisions of the By-Laws, presents the following nominations for the elective officers of the College for 1936–1937.

President-Elect, James H. Means, M.D., Boston, Massachusetts.
First Vice-President, O. H. Perry Pepper, M.D., Philadelphia, Pennsylvania.
Second Vice-President, David P. Barr, M.D., Saint Louis, Missouri.
Third Vice-President, Walter L. Bierring, M.D., Des Moines, Iowa.

Respectfully submitted,

Committee on Nominations,
Sydney R. Miller, Chairman,
Francis M. Pottenger,
James D. Bruce,
Robert A. Cooke,
Thomas Klein.

New Life Members

Dr. Willard J. Denno, New York City, and Dr. Lewis B. Bates, Ancon, Canal Zone, Fellows of the College, are new additions to the Life Membership Roster of the American College of Physicians.

The Life Membership plan of the College is worthy of very careful consideration by each Fellow at this season of the year. The plan affords the member an opportunity of protecting his membership during his productive years and while his income is greatest, thus avoiding the burden of dues later in life. It provides for underwriting dues years in advance, but of receiving active membership throughout one's entire life. A member pays no more for Life Membership than he would pay for ordinary active membership to 65 years of age, without active membership thereafter, yet he receives active membership not only until 65, but for the balance of his life. Many members can readily afford Life Membership during their active, productive years, but, with changing conditions or ill health, find annual dues a burden in later life.

It is especially appealing to some members to take out Life Membership purely from an altruistic standpoint; namely, to make this contribution to the Endowment Fund of the College, putting the organization in position, financially, to broaden its activities along lines which are clearly suggested at this time, when there is so much conflict of thought and opinions on the subjects of medical practice, medical education, certification of specialists and other topics which are of primary interest to internists. Full details of the Life Membership plan, along with illustrations of the Life Membership Certificate, appear in the 1935 Directory of the College, pages 47 to 50.

Gifts to the College Library

Acknowledgment is made of the following gifts to the College Library of publications by members:

Fellows

Dr. Malcolm T. MacEachern, Chicago, Ill.—1 book, "Hospital Organization and Management."

Dr. Walter A. Bastedo, New York, N. Y.—4 reprints.

Dr. Ralph O. Clock, New York, N. Y.—1 reprint.

Lt. Col. George B. Foster, Jr., (MC), U. S. Army—10 reprints.
Dr. Benjamin H. Frayser, Lexington, Ky.—1 reprint.
Dr. D. Waldo Holt, Greensboro, N. C.—1 reprint.
Dr. D. O. N. Lindberg, Decatur, Ill.—1 reprint.
Dr. Harold C. Ochsner, Waukegan, Ill.—9 reprints.
Dr. Henry A. Rafsky, New York, N. Y.—7 reprints.
Dr. William B. Rawls, New York, N. Y.—1 reprint.
Dr. Jesse D. Riley, State Sanatorium, Ark.—4 reprints.
Dr. H. C. Robinson, Grand Rapids, Mich.—1 reprint.
Dr. Walter M. Simpson, Dayton, Ohio—1 reprint.
Dr. R. Garfield Snyder, New York, N. Y.—3 reprints.
Dr. Percy Harry Sprague, Edmonton, Alberta—6 reprints.
Dr. August A. Werner, St. Louis, Mo.—3 reprints.

Associates

Dr. C. Kelly Canelo, San Jose, Calif.—2 reprints.
Dr. Hyman I. Goldstein, Camden, N. J.—3 reprints.
Dr. W. B. Grayson, Little Rock, Ark.—2 reprints.
Dr. M. Coleman Harris, New York, N. Y.—4 reprints and one book, "Normal Facts in Diagnosis."

CORRECTION TO 1935 DIRECTORY

Dr. Charles Leonard Brown (Fellow), Philadelphia, is Professor of Medicine and Head of the Department of Medicine of Temple University School of Medicine, instead of Associate Professor of Internal Medicine, as printed in the new Directory.

Dr. Francis M. Pottenger (Fellow) delivered the second Annual John W. Bell Lecture on tuberculosis, at Minneapolis, December 2, 1935, under the auspices of the Hennepin County Tuberculosis Association and the Hennepin County Medical Society. Dr. Pottenger's title was "The Responsibility of the General Practitioner in the Tuberculosis Program of the Future."

Dr. A. C. Griffith (Fellow), Governor of the College for Missouri, was recently elected President of the Kansas City Southwestern Clinical Association.

Dr. Edward W. Krumbhaar (Fellow) Philadelphia, and Dr. Howard Dittrick, Cleveland, were appointed by the Department of State of the United States Government as delegates from the United States to the Tenth International Congress of the History of Medicine, at Madrid, September 23–29, 1935. They, with Dr. Henry E. Sigerist, Baltimore, also served as delegates of the American Association of the History of Medicine at the same Congress.

Dr. Joel J. White (Fellow), Lieutenant Commander, has been selected for, and promoted to Commander, Medical Corps, U. S. Navy. Dr. White has been detached from duty on the Staff of Commander Aircraft, Base Force, U. S. Fleet, based at San Diego, California, and assigned to duty with the Mayo Foundation, Rochester, Minnesota, for a special course in internal medicine.

Dr. Louis Faugeres Bishop, Jr. (Fellow) presented a paper on "Recent Advances in Diagnosis and Treatment of Coronary Thrombosis" on November 20, 1935, at the meeting of the Southern Medical Association in St. Louis. On the same day a paper on "A Report of Correspondence with Physicians in the Tropics on In-

vestigation of Coronary Thrombosis" was presented before the American Society of Tropical Medicine, St. Louis, by Dr. Louis Faugeres Bishop (Fellow) and Dr. Louis Faugeres Bishop, Jr.

Dr. L. D. Sargent (Fellow), Washington, Pa., was elected Councilor of the Eleventh Pennsylvania District and a Censor of the Pennsylvania State Medical Society at its last annual meeting in October.

Dr. William Egbert Robertson (Fellow) was made President-Elect of the Philadelphia County Medical Society at its last annual meeting. Dr. Robertson is Emeritus Professor of the Theory and Practice of Clinical Medicine at the Temple University School of Medicine. Dr. Louis H. Clerf (Fellow), Philadelphia, was elected Vice-President.

Sir Aldo Castellani (Fellow), formerly Professor of Tropical Medicine of Tulane University of Louisiana School of Medicine, is supervising the Italian Medical Corps in Ethiopia.

Dr. Salvatore Lojacono (Fellow), Superintendent of Morgan Heights Sanatorium, Marquette, Michigan, presented a paper on "Tuberculosis in Finns of Marquette County" at the November meeting of the Trudeau Society at Howell, Michigan.

Dr. John I. Marker (Fellow) has been elected Vice-President of the Mississippi Valley Medical Society. This Society covers the States of Illinois, Missouri and Iowa.

Dr. Fred C. Oldenburg (Fellow), Cleveland, Ohio, was recently promoted to Assistant Clinical Professor of Medicine in the Western Reserve University School of Medicine.

OBITUARIES

DR. GEORGE ELGIE BROWN

George Elgie Brown of the Mayo Clinic, and Regent of the College for two terms (1929 to 1933), died in Rochester, Minnesota, November 28, 1935, after an illness of two weeks with pneumonia. He is survived by his wife, Irma, and his mother, Mrs. Ella Brown; also by a sister, Mrs. Esther Frost, and two sons, George, Jr., a medical student at the University of Michigan, and Hugh, a student at Carleton College, Northfield, Minnesota.

He was born in Grand Rapids, Michigan, July 16, 1885, and received his degree of Doctor of Medicine at the University of Michigan in 1909. He served an internship under the late Dr. Walter Courtney at the Northern Pacific Hospital at Brainerd, Minnesota; and it was at Brainerd that he married Irma Parker July 22, 1911. Together they went to Miles City, Montana, where he engaged in an extremely active practice of general medicine, later developing internal medicine up to 1921. His interest in accurate scientific diagnoses was exemplified from the very first. He was the first to develop in that part of Montana the complicated laboratory tests such as the Wassermann reaction, and introduced the first fluoroscope. He

sought out special opportunities for clinical study, as well as extension of his knowledge in the basic sciences, as was shown by several months' study at Harvard in 1914 and at Johns Hopkins University in 1916. The war-time found him associated in France with the Rockefeller Foundation in 1918 and 1919.

Coming to the Mayo Clinic at Rochester, Minnesota, as First Assistant in medicine in 1921, he advanced rapidly in the Clinic and the Mayo Foundation (Graduate School of the University of Minnesota) to the position of Associate Professor of Medicine in 1927.

George Brown had a wide association and membership in the usual and especial medical societies. In addition to the local, county, state and national, he had membership in the American College of Physicians, American Society for Clinical Investigation, Association of American Physicians, American Association for the Advancement of Science, Central Interurban Clinical Club, Central Society for Clinical Research, Minnesota Society of Internal Medicine, Minnesota Heart Society, American Heart Association, Sigma Xi, and Phi Rho Sigma. In addition, he took an active interest, both as to attendance and program building, and was a prolific contributor—approximately one hundred and fifty articles in periodicals, systems of medicine and textbooks, and two monographs, and during his last illness and while sick in bed was working upon a number of manuscripts. His bibliography manifests the widest range of interest, as did his clinical interests and contacts; but in recent years he delved deeply into the problem of peripheral vascular disease, and in this field he became an international authority. At the time of his death he was working upon a monograph on vascular diseases and hypertension. He approached these problems evaluating the functional influence of the sympathetic nervous system, and his work is too well known to need further comment here.

He was gifted with a judicious balance of confidence in his own powers; with sufficient respect for traditional opinion, but not enough to insulate him against original thinking. This combination, fortified by a fine personal capacity to stimulate assistants and associates, led to his very productive years and the fullest utilization of his great opportunities, with the wealth of clinical material at the Mayo Clinic at his disposal. At the same time, while working as an original investigator, he was fully able to carry on as a clinician; to please and charm people, and give them the full benefit of his wide therapeutic experience. Never, however, did he lose sight of the duty he felt—to add all he could to the understanding of our medical problems. It is proverbial, in all walks of life, that many attain their ambitions by ruthless appropriation of the opportunities, the actual work, or the resources of others. Never could this be said of Dr. Brown. He beautifully exemplified the glory of our guild—the desire to share not only with humanity but with all of his fellows the best of his mind, his heart and personality. These powers helped him to become one of the best of traveling companions.

He was meticulous in his dress and personal appearance. He enjoyed relaxation, music, good food, stimulating reading, and he had a wide interest in world affairs.

It is thus, in his untimely passing, that his multitude of friends feel a crushing loss.

E. L. TUOHY, M.D., F.A.C.P.,
Governor for Minnesota.

DR. LEWIS MANN SILVER

Dr. Lewis Mann Silver (Fellow), New York City, died August 14 of a fractured skull, as a result of a fall; aged seventy-five years.

Dr. Silver was born in Brooklyn in 1860, attended Phillips Academy at Andover, Mass., and was graduated from Yale University with the A.B. degree in 1882. He received his medical training at Bellevue Hospital Medical College, graduating in 1885. He did postgraduate work in Munich and Vienna. At the time of his death he was a member of the courtesy staff of the Babies' Hospital and assistant at the Vanderbilt Clinic of Columbia University College of Physicians and Surgeons. He was the author of a number of publications.

Dr. Silver belonged to the New York County Medical Society, the New York State Medical Society, the New York Academy of Medicine, the Medical Society of the Greater City of New York, the American Medical Association and the Society of Alumni of Bellevue Hospital. He had been a Fellow of the American College of Physicians since 1921. In addition to his medical societies, he was a member of the Yale Club, the Yale Alumni Association, the New England Society, the Vermont Society, the New Hampshire Society and the Sons of the Revolution.

ROBERT A. COOKE, M.D., F.A.C.P.
Governor for Eastern New York.

DR. EDWARD W. JACKSON

Dr. Edward W. Jackson was born in Albion, N. Y., June 21, 1877, and died on October 2, 1935, in Rochester, New York, of his third cerebral hemorrhage.

Dr. Jackson graduated from Albany Medical School in 1907 and practised in Little Falls, N. Y., for three years. A severe automobile accident caused him to give up his work and after his recovery he devoted two years to study in various medical centers in Europe, notably in London with Drs. MacKenzie and Lewis. Returning to the United States he began the practice of cardiology and internal medicine in Rochester.

During the World War he served as Captain in the Medical Corps and acted as cardiologist at Camp Greenleaf and in Carlisle, Penna. After the war he resumed his work and continued as cardiologist and chief of the Heart Clinic at the Genesee Hospital, having first received his appointment

in 1913. He was a member of the state and county medical associations and of the A. M. A., the Rochester Academy of Medicine and was elected a fellow of the College of Physicians in 1924. He was a member of the Yonondio Lodge, F. and A. M. of the Damascus Temple, and the American Legion.

Cardiovascular disease forced him to give up his practise in Rochester, and during his latter years, his life was a long struggle with ill health. He went, successively, to California, Texas and Florida, attempting twice to resume a small amount of work in his specialty, but each time his reserve was insufficient, and he was forced to give up.

Dr. Jackson was a very earnest student of medicine and a man of tremendous capacity for work. His sympathetic and kindly nature endeared him to his patients to whom he gave his time and energy unstintedly; and thereby, no doubt, hastened his untimely death.

ROSCOE H. KNOWLTON, M.D., F.A.C.P.

DR. THOMAS CHALMERS

Dr. Thomas Chalmers (Fellow, 1919) deceased, November 16, 1935, was the son of an eminent New York physician, and a member of an old and important New York family. His mother was a Virginian of long American lineage and distinguished family.

Dr. Chalmers received his preliminary education in various private schools in and about New York City, and finally entered Princeton University, from which, however, he did not graduate. During his youth he was deeply interested in athletics, and took an active part in school and college work of this character. He graduated in medicine from Bellevue Hospital Medical College in 1897; substituted for a time on the Third Division of Bellevue Hospital, afterward serving in one of the out-patient departments of that institution.

In his youth Dr. Chalmers became a member of Company F of the Seventh Regiment of the New York National Guard, and remained with this organization at the time of the Spanish American War when he was transferred to the Twelfth Regiment of the New York National Guard as Captain and Assistant Surgeon. He served with this organization and on the Brigade Staff in Puerto Rico, and remained with the Army during the Philippine Wars, serving with distinction, and with the rank of Major, Medical Department.

On his return from the Philippine Islands, he again opened practice in West Ninth Street, New York City, where he remained until the formation of the colony at Forest Hills, Long Island, and he was one of the earliest physicians in this colony, and did much to establish a high standard of ethical and professional life in this part of Long Island.

Dr. Chalmers was actively interested in medical politics and for many years was a delegate to the American Medical Association. He was presi-

dent of the Queene County Medical Society, and was largely instrumental in the building of the Queene County Medical Building. He acted on numerous committees in connection with the health activities in this part of Long Island, and was a member of the New York Academy of Medicine, of the Advisory Council of the Commissioner of Hospitals, and on numerous other committees of professional organizations.

Dr. Chalmers married Miss Elizabeth Ducat on August 1, 1911. He was the father of three children.

Dr. Chalmers was well known for his high professional ability, his public spirit, his generous friendships, particularly to the younger members of the profession, and for his unswerving devotion to the highest standards of ethical medical practice. More than usual he possessed the power of attracting friends, both in and outside of his profession. Up to the very day of his death, he was actively engaged in public duties of many kinds beyond that which he gave to his own profession, and his patients. He was a fine citizen, a good soldier, and a high representative of his profession.

HARLOW BROOKS, M.D., F.A.C.P.

DR. ALEXANDER MCNIEL BLAIR

Dr. Alexander McNiel Blair was born in Buffalo, N. Y., July 30, 1873, and died at his home in Southern Pines, N. C., November 27, 1935.

Receiving his early education in the public schools of Buffalo and Niagara University, he graduated from the Medical Department of the University of Niagara in 1897. He settled in Southern Pines, N. C., in 1903, where he was actively engaged in practice save for the summer months, which he spent in Bethlehem, N. H., also in active work. His postgraduate work was done at Harvard University, Polyclinic Postgraduate Hospital in Philadelphia, Children's Hospital in Boston, and the Royal Victoria Hospital in Montreal. He was a member of the Volunteer Medical Service Corps during the World War, and at the time of his death was a member of the staff of the Lee County Hospital, Sanford, N. C. He became a Fellow of the American College of Physicians in 1925, and in addition held membership in the Moore County Medical Society of which he was President; the N. C. State Medical Society; the Tri State Medical Society; and the Southern Medical Association, as well as being a Fellow of the American College of Radiology.

Dr. Blair was actively interested in social and civic matters in his community, was a director in the Citizens Bank & Trust Co., and a member of the Presbyterian Church. His chief medical interests were diseases of the chest and stomach, though his work was not entirely limited to these phases of internal medicine. At the time of his death, he was the oldest practitioner in service in Southern Pines.

C. H. COCKE, M.D., F.A.C.P.,
Governor for North Carolina.

DR. ALBERT EDWARD ROUSSEL

Albert Edward Roussel (Fellow) was born in Philadelphia, September 17, 1863. He attended public and private schools and also studied under private tutors, later passing entrance examinations, admitting him to Annapolis. In 1882 Dr. Roussel was graduated from the Jefferson Medical College of Philadelphia; he served as interne in the Philadelphia Orthopaedic Hospital and Infirmary for Nervous Diseases, 1882–83; interne, Philadelphia General Hospital, 1883–84; served as externe in neurology, Hospital de la Salpetiere, Paris, 1885–87, and as externe in internal medicine and venereal diseases, St. Louis Hospital, Paris, 1887–88.

In 1888 Dr. Roussel pursued postgraduate studies in neurology and internal medicine at Heidelberg, Berlin, London and Paris. Upon his return to America he was appointed lecturer in physical diagnosis, Medico-Chirurgical College (1889–90); he became Associate Professor of Medicine and Clinical Medicine in the same institution in 1900, a position which he held until the merger of the Medico-Chirurgical College and Hospital with the University of Pennsylvania in 1916. He was elected Assistant Professor of Medicine in the University of Pennsylvania Graduate School of Medicine in 1916, and in 1920 was elected Professor of Medicine, ably filling that chair until 1932, when he became Professor Emeritus.

Dr. Roussel had served as Visiting Physician to the Polyclinic and Howard Hospitals, and held the position of President of the Staff at the latter institution for a number of years. He was also Visiting Physician to the Eagleville Sanitarium and to the French Consulate and Foreign Benevolent Society of Philadelphia. During the World War he became a member of the Medical Advisory Board and Special Medical Examiner for the French Government for the State of Pennsylvania. In 1907 Dr. Roussel received from the Government of France, the decoration, Officer d'Academie, and in 1924 also that of Chevalier de la Legion d'Honneur, from the same source.

Dr. Roussel was an honored member of numerous medical organizations, e.g., the Philadelphia County Medical Society, the Medical Society of the State of Pennsylvania, the Philadelphia Pediatric Society, the American Medical Association (Fellow), and the American Association for the Advancement of Science. He was President of the American Therapeutic Society in 1929, and First-Five-President of the Philadelphia Medical Club, and since 1916 a Fellow of the American College of Physicians. Dr. Roussel contributed a number of articles to current medical journals and he was the first to point out that Brill's disease and typhus fever were the same disease.

Dr. Roussel had an attractive personality and his presence would cast a shadow of dignity over any gathering of physicians. From personal observation, during frequent and more or less prolonged contacts, the writer is convinced that he had a clearly demonstrated ability for straight thinking

and reliable clinical observation that enabled him to reach an accurate diagnosis. His services in the capacity of teacher were highly appreciated by the Board of Trustees of the University of Pennsylvania, as shown by the fact that upon being retired from his professorial duties he was immediately made Emeritus Professor of Medicine. His career as a whole is destined to endure for a long time in the minds of his pupils and medical practitioners who sought his services as a consultant. The subject of this sketch was quite familiar with French medical literature, on which he drew freely while teaching his medical classes.

Dr. Roussel was a member of the Board of Governors of the Penn Club, with which he was prominently connected during many years. He was fond of hunting and, exceedingly so, of fishing.

Dr. Roussel is survived by his widow, Mrs. Albert E. Roussel, who was a Miss Finn, and belonged to a socially prominent family of Baltimore, a son, Albert E. Roussel, Jr., and a daughter, Mrs. J. Graham French.

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NOTES ON MEDICAL EDUCATION AND MEDICAL INSTITUTIONS IN MICHIGAN

THE approaching General Session of the American College of Physicians, which is to be held in Detroit and in Ann Arbor, will give to the members of the College an opportunity to acquaint themselves with the present status of medical education and of medical institutions in the two chief medical centers of the State of Michigan. This approaching event should, therefore, lend interest to the following brief sketch of the development of the schools of medicine and of the hospitals which will furnish the clinical features of the program.

The long and stormy history of the early settlements and trading posts in the wilderness which has since become the State of Michigan, punctuated by warfare between the white settlers and the Indians, and between the forces of the French, the English, and later the Americans, contains little that is pertinent to the later development of medical institutions. Though Detroit was settled over two hundred years ago, the great hospitals and schools now existing were all founded within the last century.

Yet, lest the medicine and surgery of those earlier pioneer days in the wilderness should be too readily considered as unimportant, it should suffice to recall that it was towards the close of this period (1822), when Michigan was still a Territory, that William Beaumont, a surgeon in the United States Army stationed in the post at Mackinac, began his long series of scientific observations and experiments on gastric function on the trapper, Alexis St. Martin, who had been left after recovery from a gunshot wound with a permanent gastric fistula. This classical investigation must be looked upon as Michigan's first great contribution to scientific medicine. It still ranks in world medical history as one of the major advances in our knowledge of human physiology.

The history of medical education in Michigan is essentially that of the development of the medical school of the University of Michigan at Ann Arbor and that of the various medical schools in Detroit which have been continued as the recently formed Wayne University College of Medicine.

During the era of proprietary medical colleges, small schools were organized at various times in Detroit and other cities of the state, but they were short lived and of little importance.

The University of Michigan Medical School opened its doors to students in 1850 at Ann Arbor, and in 1869 the Detroit Medical College was incorporated. For half a century a fusion of these institutions was under consideration. Ann Arbor, in those earlier years a small city, had limited clinical facilities and, although the medical school was outstanding in the quality of its preclinical departments, many medical men both in Ann Arbor and Detroit believed that medical education in Michigin would be advanced

by the attachment of the Detroit school, with large hospitals and a wealth of clinical material under its control, to the Medical Department of the University.

From the early eighties a number of conferences took place between the faculties of the two colleges looking to an amalgamation. The last conference met with the Council on Medical Education of the American Medical Association in Detroit in 1916.

A plan of union was proposed by the Council which was accepted by the Regents of the University and the Trustees of the Detroit College. The entry of the United States into the World War arrested the negotiations and they were not resumed. After the war the University of Michigan built its great teaching hospital and it now has the clinical facilities necessary to give a well rounded medical education.

Wayne University College of Medicine

The first attempt to give systematic medical instruction in Detroit was the organization in 1864 of a preparatory medical school by the staff of Harper Hospital, which was then used by the Government as a hospital for wounded soldiers of the Civil War. The instruction was almost entirely

Fig. 1. Wayne University College of Medicine.

clinical. The venture was a success and in 1869 the school was expanded and incorporated as the Detroit Medical College, with a faculty of fourteen members.

Two of the pavilions of Harper Hospital were remodeled and made the college building. Harper and St. Mary's Hospitals, with a college out-patient department, furnished the material for clinical teaching. The success of the college and the professional advantage which a teaching position may give excited the envy of other medical men of the city. In 1879 a rival college, the Michigan College of Medicine, was organized and, after a stormy

period of competition, the two institutions amalgamated in 1882, under the name of the Detroit College of Medicine.

The charter of the Detroit College of Medicine expired in 1913. Under a new charter and name, the Detroit College of Medicine and Surgery, the college was reorganized with faculty, equipment and curriculum brought up to modern requirements. The institution, however, did not have an adequate endowment and it had difficulty in maintaining the desired standard of medical education. In 1918, in order to save the college, its charter and property were taken over by the city. This ended its proprietary character and it became a unit of the public school system of Detroit under the control of the Board of Education.

The City of Detroit established Wayne University in 1933, and the medical college became the medical department of the University in 1934, under its present name, Wayne University College of Medicine.

Through all its changes in name and administration the present institution is a direct continuation of the Detroit Medical College organized in 1869.

The municipally owned Receiving Hospital and the Herman Kiefer Hospital, with a combined capacity of 2,050 beds, are the main teaching hospitals of the college.

The Receiving Hospital

The Receiving Hospital is operated by the City of Detroit and supervised by the Public Welfare Commission. It was founded in 1915 for the care of the indigent and emergency cases. It was re-organized in 1921 into a general hospital to include all services except obstetrics and contagious diseases, and was enlarged to its present capacity of 650 beds in 1927. The hospital still maintains a completely equipped emergency department supervised by the staff physicians. During 1934, 62,984 cases received treatment in the emergency room, 20,892 of which were subsequently hospitalized. These hospital admissions were distributed among the different services as follows:

General surgery	6564
Psychiatry	5653
Medicine	5252
Urology	1039
Gynecology	1609
EENT	1007

The hospital also maintains an out-patient department for the follow-up care of discharged patients, to which there were 106,692 visits during 1934. The hospital also houses the City Physician's Clinic which during 1934 had 368,239 visits. Much of this clinical material is utilized for teaching purposes.

The Receiving Hospital is the chief teaching unit of the Wayne University College of Medicine. Senior students serve as clinical clerks seven

hours daily for a total of twelve weeks in internal medicine, including psychiatry, neurology and dermatology, for four weeks in gynecology and for eight weeks in general surgery, including urology, orthopedics, and proctology. Junior students are taught physical diagnosis and pediatrics on the wards, and surgery and internal medicine in the out-patient department. Obstetrics and contagious diseases are taught at the Herman Kiefer Hospital.

The Herman Kiefer Hospital

The Herman Kiefer Hospital is a specialized institution, having services for all stages of tuberculosis in any form, all acute communicable diseases and maternity cases. There are 500 beds for contagion, 65 maternity beds and 65 bassinets, and 763 beds for tuberculosis. The institution is municipally owned and operated by the Board of Health.

Fig. 2. The Herman Kiefer Hospital.

The contagious service is built on the unit, or pavilion plan, and the first building was erected in 1910. Construction of the new tuberculosis unit was begun in September 1927, and the building was opened for the reception of patients in December 1928.

This unit, with a capacity of 680 beds, is devoted to the care and treatment of tuberculous patients, who are admitted through the tuberculosis clinic of the Detroit Department of Health, housed in this building.

The structure is seven stories in height. On the first floor are the administrative offices, the social service department, library, record room,

physicians' offices, offices of the nursing executives, tuberculosis clinic and health department laboratories, as well as a modern and well equipped x-ray department.

The second, third, fourth, fifth and sixth floors are devoted to the housing of patients. The rooms are either single rooms or for two patients, there being no wards, and most of them have porches. In fact, about 80 per cent of the patients can be placed on porches at one time. Each room, in addition to having prettily decorated furniture, is equipped with a radio head set. A microphone placed in the auditorium will enable speakers to give health talks to the whole patient population.

The surgical service occupies the entire seventh floor, excepting the wings, which are devoted to heliotherapy. There are five operating rooms, one of which has an amphitheater which seats 50 persons. Advances in the study and treatment of tuberculosis have brought forth corresponding advances in tuberculosis surgery, and the instrument, dressing and sterilizing rooms on this floor are equipped in the most up-to-date manner.

The space devoted to heliotherapy is divided into two sections, one side for women and the other for men. Each section is divided into compartments, one to be used for artificial sunlight and equipped with carbon arc lamps, and the other with an open roof for treatment by direct sunlight. Ultra-violet ray transmitting glass is also used in all of the patients' bedrooms.

The value of the grounds, buildings and equipment is $9,000,000.00. Operating expenses are in excess of one million dollars per year.

The hospital is a part of the teaching service of the Wayne University School of Medicine and affiliates with the various general hospitals in teaching their internes contagious diseases, tuberculosis and obstetrics. It also has a three-months' course in contagious diseases and tuberculosis for senior nurses, and has affiliations with 16 different hospitals.

In addition to the Wayne University College of Medicine and its two chief hospitals the members of the College will be interested in a number of other medical institutions in Detroit which will contribute valuable features to the program of the meeting.

Harper Hospital

Harper Hospital, one of the largest and oldest institutions in the city, was founded in 1859 through the generous gift of Walter Harper, whose name the hospital bears. At that time, an additional contribution was made by Nancy Martin, who gave a tract of five acres on Woodward Avenue (on which she had a market garden), together with other lands, to the new institution. During the Civil War, the Federal Government decided to establish a hospital for soldiers and sailors in the city, and the land was leased to the government for this purpose. The wooden buildings which

FIG. 3.

were then erected housed the sick and wounded soldiers until 1865, when the buildings were turned over to the trustees, and the institution has been conducted as a general hospital ever since. In continuation of the tradition of war-time service, Base Hospital No. 17 was sponsored by Harper Hospital in 1917. It went overseas in July of that year, and was stationed in Dijon until 1919. This reserve unit has been continued as 17th General Hospital.

With growth of the city, and under the guidance of a Board of Trustees which has ever been keenly interested in medical progress, expansion followed, and in 1883 the new building (facing John R. Street) was completed. Later years saw the completion of many other units which were made possible by the generous gifts from citizens. In 1913, the Hudson Building (containing private rooms and wards), and the Buhl Building (housing the out-patient department) were completed. In 1918, a new operating pavilion was occupied, and 1928 saw the completion of the eight story building facing Brush Street.

The Farrand Training School for Nurses (one of the first established in this country) was opened in 1883, at first occupying the "Swain Home." As these quarters became inadequate, McLaughlin Hall was erected in 1921 to house the nursing staff and pupil nurses.

The laboratory, equipped for both routine work and research work, occupies the entire seventh floor of the center building. The department of roentgenology occupies extensive quarters on the first floor. Its equipment includes super-voltage therapy apparatus (700 K.V. Constant), as well as experimental x-ray diffraction and neutron-ray apparatus.

The out-patient department was formally established in 1883; it outgrew its old quarters, and in 1914 occupied the new Buhl Building. About

10,000 to 12,000 new patients are treated yearly, the number of daily visits being 300 to 400.

The hospital is completely equipped as a general hospital, and receives every type of case, excepting contagious diseases. It has a capacity of 625 beds, including private rooms and endowed ward beds.

FIG. 4. Harper Hospital. Building erected in 1928.

HENRY FORD HOSPITAL

In the year 1909 it became manifest to the medical profession and public-spirited citizens of Detroit, that the city's hospital facilities had not kept pace with the amazing progress made in other fields. There was then formed the "Detroit General Hospital Association" of which body Mr. Henry Ford was a member, and of which he later became Chairman of the Board of Trustees. The purpose was the development of a hospital for Detroit under the name of the "Detroit General Hospital."

Two years later, namely, in 1911, ground was broken for the new institution and a building program begun. The work did not progress as was expected, so that with incompleted buildings, and with about one-third of the needed sum in hand, the original plan was enabled to continue only through Mr. Ford's vision and generosity.

In June 1914, five years after the incorporation, and three years after the building program had begun, Mr. Ford mad[illegible] offer to take over full responsibility for the development of the new [illegible]al. This offer was immediately accepted.

These chronological details tell the story of how the Henry Ford Hospital came into existence.

The Henry Ford Hospital was incorporated under the Laws of the State of Michigan on September 15, 1915. It is a general hospital with a bed capacity of 600, offering services to both in-patients and out-patients in all branches of medicine, surgery, pediatrics and obstetrics.

The hospital has been registering about 15,000 persons as patients a year. Recently the 227,300 mark was passed.

In 1925 a School of Nursing and Hygiene was opened and operated in conjunction with the hospital.

In the laboratories of the hospital facilities for research have been provided, and from these laboratories as well as from the clinical departments a program of unusual interest may be expected.

The Grace Hospital

The Grace Hospital was founded in 1888 by a group of public spirited citizens who contributed the cost of the original buildings and established an endowment fund of $100,000, which was later increased to $300,000. The site of the Hospital, at the corner of John R. St. and E. Willis Ave., was contributed by one of the founders.

In 1910 an addition of four stories was built which included an x-ray suite, a group of operating rooms, a pediatric service, and a group of laboratories, together with accommodations for 50 additional private and semi-private patients.

The growth of the city soon placed added responsibilities on the Board of Trustees. In 1919, directly after the War, the Board instituted a construction program to cover a period of ten years and to involve the expenditure of $2,500,000.

Between 1914 and 1930 the original Main Hospital Building on John R. St. was extensively reconstructed and improved. An obstetric ward and a urological unit were provided, and the roentgenologic equipment was modernized. In 1926 a third addition to the Main Hospital was built, which included an out-patient clinic service and 30 additional private rooms.

In 1929 a campaign for $1,850,000 was carried through successfully for the purpose of increasing the bed accommodations in the main hospital, and as a result of this campaign the Memorial Building of the main hospital was constructed on the Brush St. frontage.

In 1912 a member of the Board of Trustees donated a site and a building on West Grand Blvd., as a memorial to his deceased daughter. After alterations, 57 beds were provided, and thus a branch hospital, known as the

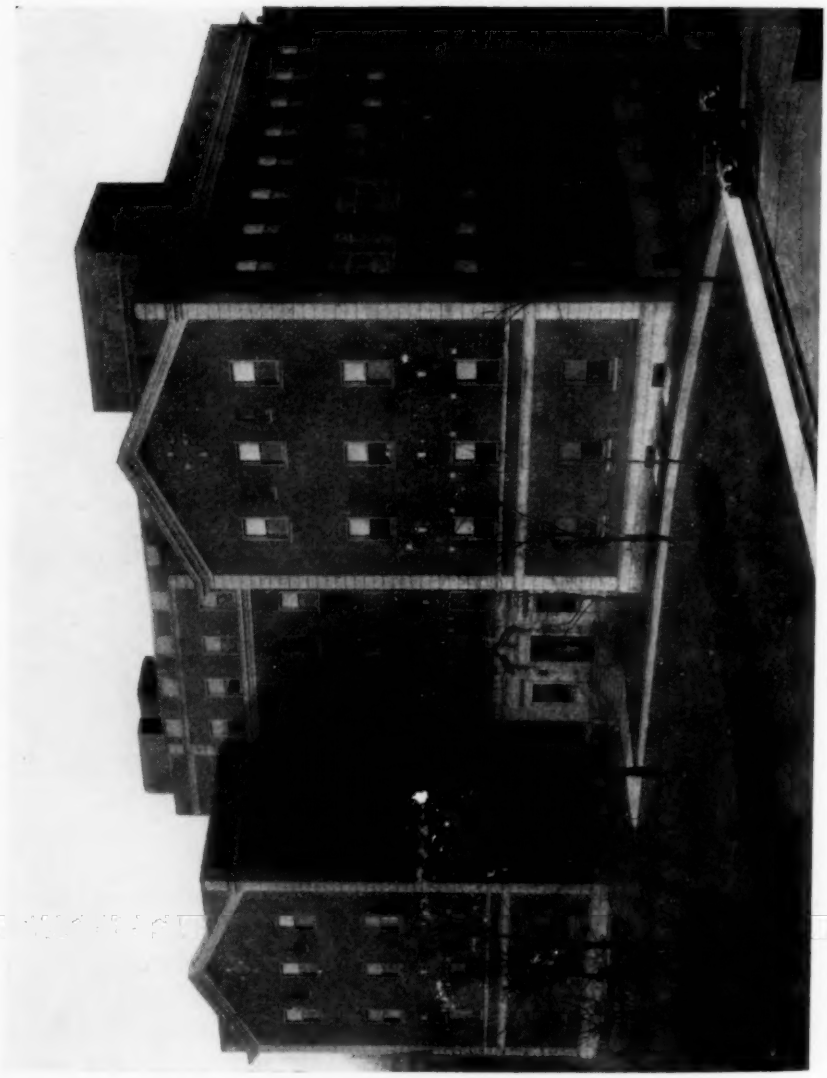

FIG. 5. The Grace Hospital.

Miriam Memorial Branch of the Grace Hospital, was opened, which has given a much needed community service to the West Side for many years.

In 1919 a Nurses' Home for the Miriam Memorial Branch was built. In 1929 the first unit of a new hospital building at this branch hospital was constructed.

In 1889 the Training School for Nurses was organized and the first Nurses' Home, constructed later, was the gift of a public spirited woman.

In 1931 a new Nurses' Home was erected at a cost of $600,000. This addition was occupied first in 1932.

The building of the new Nurses' Home permitted the expansion and improvement of the School of Nursing, with installation of modern pedagogic equipment. The development of the Training School and the standards in nurse-teaching have kept pace with the growth of the Hospital.

In the 47 years of its existence, the Hospital has cared for over 325,000 bed patients. In 1935 the capacity of the Hospital was 527 beds. In 47 years it has given relief to over 1,000,000 ambulatory indigents. The cost of the latter has been partly provided by the Detroit Community Fund through the Council of Social Agencies.

For more than two generations some of the leading representatives of the medical and surgical profession have served on the staff of this Hospital, and many of the prominent citizens of Detroit have been members of its Board of Trustees.

Children's Hospital of Michigan

On November 12, 1886, a group of Detroit women who were interested in child welfare met and organized the Children's Free Hospital Association. The first hospital work of this Association was begun on a ward in Harper Hospital. Two years later, however, a temporary hospital was established in a house at Seventh and West Fort Streets. In 1896 a generous gift from a prominent citizen of Detroit made possible the construction and endowment of the present building. In 1922 a merger was effected with the Michigan Hospital School which possessed a building in the country at Farmington, and the merged institution assumed the name of the Children's Hospital of Michigan. This made it possible for the acute medical and surgical cases to be cared for in the city hospital, while the Hospital School building at Farmington was used as a convalescent home.

Since this merger, many new facilities have been added. New wings have been constructed to the main hospital and additional buildings have been erected at Farmington. A nurses' home, a new out-patient department, a new roentgenologic department and new laboratories have all been added to the facilities of the city hospital. The city branch now has a capacity of 239 beds and the country branch has 240 beds. The hospital cares for all illnesses of children excepting pulmonary tuberculosis and contagious diseases. The hospital is governed by a permanent Board of Trustees. It

is supported by the income from its endowment fund, contributions from parents, receipts from the care of city, county and state patients, and by funds allotted by the Detroit Community Fund.

FIG. 6. Children's Hospital of Michigan.

In 1934, 6,449 patients were admitted to the hospital and 73,822 days' care were given; 7,800 new patients were cared for in the out-patient department and 84,000 patients' visits were made there; 550 patients were admitted to the Convalescent Home and were given 65,846 days' care.

The hospital maintains a school for teaching pediatric nursing to senior students from accredited training schools and to postgraduate students.

THE WAYNE COUNTY MEDICAL SOCIETY

The Wayne County Medical Society was organized as a branch of the Michigan State Medical Society in 1849. The law under which it operated was repealed in 1851. The Detroit Medical Society functioned as its successor until 1866, when it was reorganized under its old name. In 1876 the Society was incorporated and had an active period of several years. Professional interest became divided by the organization of the Detroit Academy of Medicine by the faculty of the Detroit Medical College and the Detroit Medical and Library Association.

The Wayne County Society was kept alive by a small socially congenial group.

The Medical and Library Association, at that time the dominant society of the city, was compelled, by the adoption of the present membership requirements of the American Medical Association, to disband and transfer its membership to the Wayne County Society, which then became the powerful organization that it is today. In 1909 it purchased a property and added to

it a library building and an auditorium. Later the library was put in charge of the public library of the city, and with the organization of Wayne University it was transferred to the medical department and is now housed in the college building. In 1932 the Society removed to its present building acquired through the generosity of a public minded citizen. It is now the center of medical activity in the city. It has a membership of over 1,500, the fourth largest county medical society in the country. Its club features

FIG. 7. The Wayne County Medical Society Building.

make it a popular daily meeting place for medical men. Through its various committees it takes a prominent part in civic affairs of medical interest, especially in the fields of social service, the medical care of the indigent and the safeguarding of the proper interests of the medical profession.

THE UNIVERSITY OF MICHIGAN MEDICAL SCHOOL, ANN ARBOR *

The University was founded in 1817 when the Governor and the Judges of the Territory of Michigan, which then had a population of less than

* Contributed by Frederick G. Novy, M.D., ScD., LL.D., Dean Emeritus of the Medical School.

7,000, passed an Act establishing the Catholepistemiad or University of Michigania. This Act provided for thirteen professorships, designated as didaxia, one of which was specified as iatuca or medical sciences. The sponsors of the Act were John Monteith, a Presbyterian minister, Gabriel Richard, a French priest, and A. B. Woodward, a Judge. The germ of the idea of a medical school thus was incorporated in the proposed structure; possibly the sponsors had in mind the case of Nathan Smith who first at Dartmouth and later at Yale constituted the whole medical faculty.

A new Act was passed in 1821, repealing the former one, and creating a University of Michigan at Detroit. The Trustees of the new University did little more than to secure from Congress the grant of valuable lands for its support, some of which they promptly sold at a very low figure.

On January 26, 1837, Michigan, then having a population of about 100,000, was formally admitted as a State into the Union. Shortly before this date, the Superintendent of Public Instruction, the Reverend J. D. Pierce, a graduate of Brown, presented a comprehensive educational plan, based on the Prussian system. As a result, the Legislature of the new state, on March 18, passed the Organic Act establishing the University of Michigan; and two days later another Act was passed locating the University at Ann Arbor. In the first Act it was specified that the University was to consist of three departments: The Department of Literature, Science and Arts; the Department of Law; and, the Department of Medicine. The first of these departments was opened in September 1841.

The Department of Law, perhaps, should have been the next to be established, but in January 1847, a petition was presented to the Board of Regents asking for the organization of the Medical Department. Owing to an adverse legal opinion no action was taken at the time. However, a year later, the Board formally adopted a report whereby the School was established, money was appropriated for a laboratory building, and professors were appointed. After some delay, due to lack of funds, the Medical Building was finally completed and when its doors were opened to students in the fall of 1850, a faculty of five professors were on hand to give instructions.

The Medical Department was the first professional school established at the University. This example of Michigan in providing for medical education at a university was taken up, largely by the newly formed western states. At the present time 30 state universities have medical schools. Moreover, the new Medical School was an integral part of the University and not a merely nominal connection as was often the case. The professors were salaried and the equipment was provided by the University.

Because of its financial independence, the new medical school was able to carry out policies which otherwise might have been very difficult. Thus, it started out with a course of two years of six months each. In those days the course of instruction in the medical colleges of the country, almost without exception, extended only over four months. The apprentice system was

FIG. 8. University of Michigan Hospital.

in vogue and since the instruction was given largely by lectures and recitations it was required for graduation that the student exhibit evidence of having pursued the study of medicine and surgery for the term of three years with some respectable practitioner of medicine (including lecture terms). This preceptorial system lasted for three decades.

FIG. 9. University of Michigan Medical School, West Medical Building.

In 1878, the course was lengthened to two years of nine months each, and in 1880 to three years of nine months each. This increase in time was brought about by the introduction of laboratory courses and hospital instruction. In 1890, the course was extended to four years of nine months each, thus permitting the further development of a graded course for the teaching of the rapidly growing basic sciences and the expanding clinical work. Another step taken at this time was the establishment of the first Combined Course in Arts and Medicine. This combination, though criticized at the time, has since been generally adopted by other universities.

The entrance requirements for the Medical School in 1850 were much the same as those for entrance to the Literary College but gradually they were modified so that only " the elementary branches of an English education " remained.

With the increase in the length of the course and the teaching of the new sciences it became evident that the requirements for admission should be raised. Hence, it was that in 1890 they were advanced to a diploma from

the classical course in an approved high school, and a little later, in 1896, the requirement of certain languages and science subjects was made effective.

In 1909, the minimum requirement for admission was placed at two years of collegiate work; and in 1929, this was increased to 70 hours, and, in 1931, it was advanced to 90 semester hours.

The School which opened in 1850 with five professors now maintains a staff of 24 professors, 19 associate professors, 23 assistant professors, 78 instructors and 82 assistants, or a total of 226. The dean is A. C. Furstenberg.

Laboratories were not a conspicuous part of the medical schools of 1850. True, rooms for dissection were provided but the other sciences were either in their infancy or as yet unborn. The chair of Anatomy at the University was first filled by Moses Gunn who later became professor of surgery and eventually was called to Rush Medical College. He was followed by Corydon L. Ford who held the position for 40 years. Then came J. P. McMurrich who after 12 years of service accepted the chair at Toronto; his successor was G. L. Streeter who after a few years left to take charge of the newly organized Carnegie Institution in Baltimore. The department was then combined with histology under G. C. Huber and R. E. McCotter.

Histology as an offshoot of anatomy was recognized in 1877 as a separate study when a laboratory was equipped, and in 1879 by the appointment of C. H. Stowell, but in 1889 it was temporarily combined with physiology under W. H. Howell. After a short time the work was taken over by G. C. Huber who carried on until his death in 1934.

At Michigan, some laboratory chemistry was at first given in the old Medical Building and with such success that it led, in 1856, to the construction of the first chemical laboratory in a state university, if not the first in the country. The original small building was repeatedly enlarged and finally in 1909 the present laboratory was completed and occupied. It was in the old chemical laboratory that physiological chemistry developed in the seventies. The first chairs in this subject were filled at Yale by Chittenden and at Michigan by V. C. Vaughan at about the same time. After a few years the chair was combined with hygiene, and Vaughan held the dual position until his retirement in 1921. His successor in physiological chemistry is H. B. Lewis.

Physiology was first an appanage of anatomy under C. L. Ford and a laboratory was established in 1877, but the modern experimental phase began with Henry Sewall who entered on his work as professor in 1881. Because of ill health he was forced to retire and was succeeded in 1889 by W. H. Howell who held the position until 1892 when he went to Harvard and a year later to Johns Hopkins. He was followed by W. P. Lombard who retired in 1923 to be succeeded by R. Gesell.

Pathology was likewise in the early days combined with another chair,

namely medicine, under A. B. Palmer. After his death in 1887, an independent chair was created, under H. Gibbes, and laboratory work was instituted. In 1895, the chair was recombined with medicine under George Dock, the actual instruction being carried on by A. S. Warthin who filled the chair until his death in 1931. His successor is C. V. Weller.

Materia medica and therapeutics were at first tied up with chemistry, later passed on to anatomy, physiology, ophthalmology and, again, with medical chemistry, or given independence for a short time. In 1890, however, the chair of Pharmacology was established under J. J. Abel who, in 1893, left to join the Johns Hopkins faculty. He was followed by A. R. Cushny who, in 1905, was called to London and later to Edinburgh. His successor is C. W. Edmunds.

In 1888, the Hygienic Laboratory was built from a special appropriation of the Legislature, and the first systematic instruction in bacteriology given in this country was begun under F. G. Novy who retired in 1935 and was succeeded by M. H. Soule.

It will be seen from the above that the importance of the sciences was early recognized and every opportunity was given for their development. Today the School is provided with three large and commodious buildings for instruction and research in the basic sciences.

Of clinical instruction in the present sense, there was but little during the first two decades. At first, some effort was made to give such instruction in a summer session in Detroit but this was attended with little success. The location of the medical school in a small city, such as Ann Arbor at that time, was decidedly unfavorable from a clinical standpoint and repeated attempts were made to have the school removed to Detroit but with no success. In the absence of hospital facilities the clinical staff invited physicians to bring in their patients on three mornings in the week for diagnosis and demonstration. This custom had a beneficial result for before long patients did present themselves at these modest clinics. They were then brought into the lecture room of the old Medical Building where they were examined before the class and, if need be, operated upon and then carried to a private house for subsequent care.

In 1869, the beginning of a hospital was made when one of the four professors houses on the campus was fitted out for that purpose. This did not relieve the situation materially and, in 1875, the Legislature was prevailed upon to appropriate a small sum of money for a wooden pavilion hospital, of the type used during the Civil War, which was to be connected with the former building. It was argued that a hospital would become so infected in time that it would be necessary to burn or demolish it and replace it with a new one. However, the new pavilion hospital proved its need and the Legislature of 1879, 1881, and 1883 was prevailed upon to make further appropriations, at no time exceeding $7,000, for additions such as a women's ward, a ward for eye and ear cases, and a clinical amphitheater.

By 1889 the wooden hospital on the campus had more than reached its

limit and again the legislature was called upon to relieve an intolerable situation. This time it appropriated what seemed to be a very large sum ($100,000) for the erection of a new brick hospital on the hill overlooking the Huron River. In the following years repeated additions and extensions were made, but the conditions became far from satisfactory because of the increasing demand for medical and surgical service on the part of the citizens of the state. Serious thought was given to the building of a new and thoroughly modern hospital. The Legislature was again appealed to and this time a grant of one million dollars was made. Before construction was entered on we were involved in the World War and the matter was postponed. After the War it was clear that the amount appropriated would be insufficient and further requests were presented to the Legislature with the result that enough funds were provided to erect the present new hospital which was opened in 1925. It has a capacity of 835 beds and since some of the old buildings have been retained the entire hospital has a capacity of 1,312 beds. It is essentially a teaching hospital and as such is unique. The most recent addition is a therapeutic pool primarily intended for cases of poliomyelitis.

A state psychopathic hospital was erected on the hospital grounds in 1906. It was the first University building for psychiatric teaching to be established in this country. It has a capacity of 62 beds and in the near future it will be enlarged to provide 90 beds.

Adjoining the main hospital is the Simpson Memorial Institute for Medical Research, opened in 1927, and primarily devoted to the study of pernicious anemia and other blood diseases.

As might be expected, of the five original appointments to the faculty, three were clinical, namely, surgery, medicine and obstetrics, including diseases of women and children. The specialties were to come later.

In surgery, in the interval of 63 years between Gunn and the present incumbent, F. A. Coller, there were six professors. The surgery staff at present numbers 37 of whom 10 hold the rank of professor. With two exceptions all are on full time. Besides general surgery, there are subdivisions of neuro-surgery, orthopedics, thoracic surgery and urology.

The head of the Department of Medicine is C. C. Sturgis who is also the eighth appointee to the chair. The staff consists of 27 full-time men, of whom 9 rank as professors.

The Department of Obstetrics and Gynecology is in charge of N. F. Miller who is the fifth to hold that chair.

Ophthalmology and aural surgery was one of the first specialties to be recognized (1872). It was divided in 1904 and the present head of the former is F. B. Fralick while the Department of Otolaryngology is headed by A. C. Furstenberg.

Neurology was recognized as an entity in 1888. This work is in charge of C. D. Camp.

Dermatology was introduced into the curriculum in 1890 and is headed by U. J. Wile.

The Department of Pediatrics was dissociated from Obstetrics in 1901 and ever since has been conducted by D. M. Cowie.

The chair of Psychiatry was established in 1906 and given to A. M. Barrett who is the present head of the Department.

Roentgenology was the last of the special chairs to be created and the work is now in charge of F. J. Hodges.

A Department of Postgraduate Medicine is maintained for the purpose of giving instruction to practitioners. Special courses are given in different parts of the state. This work is in charge of J. D. Bruce.